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*Assisted by a grant-in-aid from the Tobacco Industry Research Committee.

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*Assisted by a grant-in-aid from the Tobacco Industry Research Committee.

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Abstracts of Reports

Each recipient of a Tobacco Industry Research Committee grant-in-aid is responsible for the initial presentation or publication of the results of his research in scientific meetings or in appropriate scientific journals.

Following are abstracts, approved by the authors, of research reports, with acknowledgment of support from the T.I.R.C., that have appeared in scientific journals since the last Report and through October 1960. Titles of earlier papers by grantees abstracted in previous Reports of the Scientific Director are listed at the end of this section. The name of the scientist to whom the T.I.R.C. grant was made is given in parentheses where required.

These abstracts have been grouped under six headings: I. Cancer Research; II. Human Lung Studies; III. Heart and Circulation; IV. Psychophysiological; V. Tobacco Chemistry; and VI. Other Studies.

I. *Cancer Research*

"A STUDY OF THE SENSITIVITY OF THE MOUSE FORESTOMACH TOWARD CERTAIN POLYCYCLIC HYDROCARBONS." By Fred G. Bock and Douglas W. King, Roswell Park Memorial Institute Biological Station, Springville, New York. *Journal of the National Cancer Institute,* Volume 23, pages 833-839, October 1959. (T.I.R.C. grantee: Bock)

Purpose of study: During pilot studies of the effects of cigarette-smoke condensate on the mouse skin, a significant number of papillomas were observed in the forestomach of C57BL mice which had been "painted" once with about 1.5 mg. of 7,12-dimethylbenz(a)anthracene (DMBA), suggesting that the forestomach might serve as a test site for screening weakly carcinogenic hydrocarbons. To investigate this possibility, the effects of orally administered DMBA and 3-methylcholanthrene (MC), and also benz(a)anthracene (BA), were studied.

Procedures: C57BL mice were deprived of food for 24 hours and then intubated through the esophagus, each animal receiving 0.1 ml. of heavy mineral oil containing 0.5 mg. of test compound. Repeated doses were given to some at intervals of 3 or 7 days, and the animals were maintained without further treatment until gastric papillomas were found consistently among the animals that died. DMBA and MC groups required a period of 8 to 10 months, and the BA series were killed after 16 months, although tumors had not been found in the post-mortem material available.

Findings: A single intragastric application of 0.5 mg. of either DMBA or MC gave rise to a forestomach tumor incidence of 85% and 57%, respectively. Multiple applications totaling 4 or 8 mg. produced papillomas in all 44 treated animals and carcinomas in 6. Among 27 mice receiving 4 or 8 mg. of BA by stomach tube, 2 developed papillomas of the forestomach after 16 months, but no tumors appeared among 29 mice treated once with 0.5 mg. of BA. The data indicated that the mouse forestomach is more sensitive to single applications of carcinogens than the skin.

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"TUMOR-HOST RELATIONSHIPS STUDIED *IN VITRO:* EXPERIMENTS WITH TISSUE SLICES." By Leopold R. Cerecedo, Sister Marian Jose Smith, and Jesus Vicente, Department of Biochemistry, Fordham University, New York City; Department of Biochemistry and Nutrition, School of Medicine, University of Puerto Rico, San Juan; and College of Saint Elizabeth, Convent Station, New Jersey. *Biochemical and Biophysical Research Communications,* Vol. 3, pages 328-332, September 1960. (T.I.R.C. grantee: Cerecedo)

Purpose of study: Previous studies have shown that the presence of a tumor causes certain chemical changes in the host tissues at a distance from the tumor, which are reversed when the tumor regresses. This work undertook the study of the incorporation of thymidine-H^3 into deoxyribonucleic acid (DNA), and of adenine-8-C^{14} into DNA and ribonucleic acid (RNA), in slices of tissues of normal and tumor bearing rats.

Procedure: Lungs, liver, spleen, and kidneys were extirpated from rats bearing the Walker 256 carcinosarcoma and the Jensen sarcoma, and from normal rats, and tissue slices made. The incorporation of adenine-8-C^{14} and thymidine-H^3 into the DNA of tissues of the normal rats and carcinoma bearing rats, was determined by radioactivity counter.

Findings: Slices of liver, spleen, and lung of rats bearing the Walker tumor incorporated thymidine into DNA to a markedly greater extent than did the slices of corresponding normal tissues, whereas the kidney did not show any change. Similar results were obtained in rats bearing the Jensen sarcoma except that changes in the spleen were more pronounced. In the experiments with adenine in rats bearing the Walker tumor, the DNA in the liver, spleen, and lung showed greater activity while the kidney did not show any change. In rats with the Jensen sarcoma, the tumor caused an increase in the activity of the DNA of the liver, spleen, and lung. As to the RNA, both tumors caused a slight rise in the activity of the liver. In other tissues, a drop in the activity was usually observed. The pattern of thymidine and adenine incorporation *in vitro* by the organs of normal and tumor-bearing rats, especially by the liver and spleen, are in harmony with the results which Cerecedo et al (1959) observed *in vivo*.

Other grantors: U.S. Public Health Service and the Damon Runyon Memorial Fund.

"EFFECT OF AIR POLLUTANTS ON CILIATED MUCUS-SECRETING EPITHELIUM." By Herta M. Tremer, Ph.D., Hans L. Falk, Ph.D., and Paul Kotin, M.D., Department of Pathology, University of Southern California, School of Medicine and Los Angeles County General Hospital. *Journal of the National Cancer Institute,* Vol. 23, pages 979-998, November 1959.

"EFFECT OF CIGARETTE SMOKE AND ITS CONSTITUENTS ON CILIATED MUCUS-SECRETING EPITHELIUM." By Hans L. Falk, Herta M. Tremer, and Paul Kotin. *Journal of the National Cancer Institute,* Vol. 23, pages 999-1012, November 1959. (T.I.R.C. grantee: Falk)

Purpose of studies: Under normal conditions, the flow of the mucous stream in the respiratory tract prevents the accumulation of particulate matter on the respiratory epithelium. The movement of this stream is related

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to two factors: the whip-like action of the cilia, which provides the propelling force, and the amount and consistency of the mucus. These studies were instituted with the ultimate aim of quantitating the inhibitory effects of inhaled substances on ciliary activity and flow of the mucous stream. The first paper is concerned with the development and standardization of methods for determination of the effects on mucous flow of exposure to irritants in the polluted atmosphere and with correlation of the physiologic findings with morphologic changes of the respiratory epithelium. The second paper compares the effects of cigarette smoke with the response to irritants in polluted air.

Procedures: The measurement of mucous flow was first undertaken with the use of exteriorized and *in situ* tracheobronchial segments in anesthetized rats or rabbits; parallel studies were performed on isolated tracheobronchial segments from the same animals. It was soon found that the data were comparable both qualitatively and quantitatively. Further work was done on the esophageal tract of the frog, which was technically less complicated, because environmental agents could be introduced at room temperature. Here also, it was found that the qualitative findings were similar and extrapolatability of data was not affected.

In the first paper, the animal specimens were exposed to the test aerosols under constant conditions by two methods—one a "by-pass" method which attempted to duplicate *in vivo* conditions of exposure that exist in the major part of the tracheobronchial tree, the other by impinging the aerosols directly on selected areas in order to duplicate *in vivo* conditions occurring at bifurcations and angulations of the respiratory tract. The rate of flow and other physiologic and histologic changes were determined, and conditions prior to exposures were used as controls.

In the second study, the experiments were repeated with cigarette smoke. The smoke was diluted in a mixing chamber, and a portion was passed over the tissue by either the impingement or by-pass method. Further tests were made by applying micro drop quantities of water-soluble components of cigarette smoke to the downstream end of the ciliated epithelium specimens.

Findings: The initial response of the specimens of epithelium to natural and artificial smog, ozonized hexene-2 (in lieu of gasoline), and other individual and allied compounds usually was a transient increase in mucous flow rate, which was rapidly superseded by a slowdown in the flow rate of mucus, followed by slow recovery to the base line rate. The effect was fundamentally nonspecific since essentially unrelated chemical compounds could produce the effects. Also, the response was not species-specific. The initial increase in flow rate varied in intensity with the exposure agent, whereas the slowing and recovery periods were relatively constant, more persistent, and largely independent of the test agent.

Direct impingement of the test agents produced a more quantitively intense, though qualitatively similar, response as compared to the by-pass method. Changes in consistency of the mucus also occurred, and will be evaluated in later work. Morphologic studies revealed a marked increase in the number and activity of the goblet cells. The intensity of histopathologic changes paralleled the intensity of the abnormal physiologic response.

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In the tests with cigarette smoke, brief stimulation of epithelial flow also was followed by inhibition and recovery periods. The impingement method elicited the strongest original stimulation, but the inhibition effect was most intense after the aqueous solution test, and recovery never returned to the base line flow rate when this method was used.

Basically, cigarette smoke in all its various fractions, as well as in its entirety, primarily decreased the rate of mucous flow after a short preliminary acceleration. The deceleration persisted for a considerable period and was relatively constant for both whole smoke and its various componets. Filtration resulted in a smoke which had little or no altering effect beyond a brief initial acceleration.

The elicitation of a response to both air pollution and cigarette smoke establishes that from a physiologic point of view a hazard exists during exposure to virtually all measurable concentrations of these agents. These repetitive studies are believed to parallel the human situation.

Other grantors: U.S. Public Health Service and American Cancer Society.

"A CORRELATED HISTOLOGICAL, CYTOLOGICAL, AND CYTOCHEMICAL STUDY OF THE TRACHEOBRONCHIAL TREE AND LUNGS OF MICE EXPOSED TO CIGARETTE SMOKE. III. UNALTERED INCIDENCE OF GROSSLY VISIBLE ADENOMATOUS LUNG TUMORS IN FEMALE CF[1] MICE AFTER PROLONGED EXPOSURE TO CIGARETTE SMOKE." By Rudolf Leuchtenberger, M.D., and Cecilie Leuchtenberger, Ph.D., The Children's Cancer Research Foundation and Department of Pathology, The Children's Hospital, Boston, Mass.; and William Zebrun, M.D., and Patricia Shaffer, Department of Pathology, Western Reserve University, Cleveland, Ohio. *Cancer,* Volume 13, pages 956-958, Sept.-Oct. 1960. (T.I.R.C. grantee: Cecilie Leuchtenberger)

Purpose of study: In the course of the authors' major correlated study of the sequence of events in the respiratory tract of mice after exposure to cigarette smoke, attention was also given to the adenomatous lung tumors so frequently observed in certain strains of mice. This report deals with the incidence of grossly visible adenomatous tumors in the lungs of experimental mice and in non-exposed controls.

Procedure: A total of 397 female CF[1] mice were examined at death, between three and 28 months of age, of which 166 were non-exposed controls and 231 had been exposed daily to the smoke of one-half to eight cigarettes, at hourly intervals, for periods ranging from 17 to 600 days. The mice were not smoked on week-ends and holidays. At certain periods after exposure, the experimental mice and their controls were killed and the grossly visible adenomatous tumors were recorded.

Findings: No statistical difference was found in the frequency of the lung tumors between the controls and the exposed mice. About one-third of the mice in both groups had tumors ranging between 1 and 14 mm. in size. The histological features also were very similar in both groups. The tumors most frequently seen were benign adenomas.

When controls and exposed mice were arranged according to the age at which tumors were observed, a relationship between age and tumor incidence was apparent. With the exception that the exposed mice reached

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an incidence of 40% at ages of 8 to 10 months, compared to that at 11 to 14 months in the controls, the plotted curves for controls and exposed mice are very similar for all ages.

When mice were grouped according to length of time of exposure to cigarette smoke, it can be seen that at 11 to 28 months of age there was essentially the same frequency of adenomatous lung tumors when exposed to smoke for 17 to 99 days and for 100 to 199 days, while the tumor frequency in mice exposed from 200 to 600 days increased to 66%. However, it should be noted that non-exposed controls of the same age also had a higher tumor incidence — namely, 56% — than that found in mice exposed for 17 to 199 days.

Whether exposure to cigarette smoke may sometimes accelerate the development of the tumors cannot be answered at this time. In view of the small samples, more experiments with larger numbers of mice should be carried out in order to determine whether such a difference is significant.

"STUDIES ON THE EFFECTS OF ACETALDEHYDE ON TISSUE CELLS CULTIVATED *IN VITRO*." By Donald M. Pace and Alice Elliott, Institute for Cellular Research, University of Nebraska, Lincoln. *Cancer Research,* Vol. 20, pages 868-875, July 1960. (T.I.R.C. grantee: Pace)

Purpose of study: There is considerable interest in the possible toxicity, carcinogenicity or cocarcinogenicity of the constituents of tobacco smoke, in which acetaldehyde occurs in concentrations of 0.98 to 1.31 mg. per cigarette, depending upon the kind of tobacco. This investigation was undertaken to ascertain the short- and long-term effects of this substance upon several types of tissue cells cultivated *in vitro*.

Procedure: Four cell lines were used: Earle's strain L cells, mouse liver epithelial cells, human skin cells, and HeLa cells. Routine sub-cultures were made once a week for the first two strains and sometimes each 3 or 4 days in the latter two. Observations on the toxicity and possible influence of acetaldehyde upon rate of proliferation were made periodically, usually 48 hours after replication. Occasionally during the short-term experiments, and in all except the first series of long-term experiments, the percentage of viable cells in a culture inoculum was ascertained.

Purpose of studies: In the course of *in vitro* development of most mamskin cells exposed to 2.0 mg. acetaldehyde per ml. seemed to resemble those of the control, except for a definite granulation and vacuolization, but careful examination showed that the cells were dead. The cells began to round up and detach within a half hour when exposed to 8.0 mg. acetaldehyde. Thus, these two concentrations proved toxic to the cells in a matter of hours in the lesser and of minutes in the stronger concentrations. A second series, exposing skin, HeLa and liver cells to 1.0 and 0.01 mg. acetaldehyde, also showed toxic effects in a matter of hours in the larger concentration, as did a third series using concentrations of 0.5 and 0.05 mg. respectively.

On the basis of the short-term findings, 0.01 mg. and 0.05 mg. concentrations of acetaldehyde were chosen for the long-term studies, being the least toxic in effect. At these concentrations cell proliferation appeared to be normal or was actually stimulated (except for the liver cells in 0.05 mg./ml.), leading to these questions: Does this stimulation continue as long as the cells are exposed? Do the cells return to their normal rate of

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growth and then continue to proliferate as though no acetaldehyde were present? Is there a gradual accumulative effect of the substance that may hinder later growth?

From the results it is evident that 0.05 mg. acetaldehyde per ml. is toxic to the liver cells. The L and HeLa cells proliferated well, at least for the first few weeks, but cells exposed to this concentration never increased as much as the controls. After a period of several months, however, the acetaldehyde becomes inhibitory, and the cultures may die out because of its presence. It also appears as though those cells which showed the effects of acetaldehyde accumulation recover if placed in normal nutrient medium, unless the time of exposure to this substance had been excessive.

Other grantor: U. S. Public Health Service.

"ON THE CHROMOSOME NUMBERS OF HUMAN AMNION CELLS IN PRIMARY AND STRAIN CULTURES." By Y. H. Nakanishi, M. V. Fernandes, M. Mizutani and C. M. Pomerat, Tissue Culture Laboratory, Department of Anatomy, University of Texas Medical Branch, Galveston. *Texas Reports on Biology and Medicine,* Vol. 17, pages 345-353, Fall 1959.

"SMOKE CONDENSATES ON LUNG CELLS IN TISSUE CULTURE WITH SPECIAL REFERENCE TO CHROMOSOMAL CHANGES." By Yuh H. Nakanishi, Masahiro Mizutani and C. M. Pomerat. *Texas Reports on Biology and Medicine,* Vol. 17, pages 542-590, Winter 1959.

"THE DEVELOPMENT OF A KITTEN LUNG CELL STRAIN AND ITS CHROMOSOMES." By Yuh H. Nakanishi. *Zeitschrift für Zellforschung,* Vol. 51, pages 138-151, 1960.

"THE DEVELOPMENT OF A NEAR-DIPLOID *IN VITRO* STRAIN FROM A SMOKE-CONDENSATE INDUCED MOUSE TUMOR." By Masahiro Mizutani, Yasushi Ohnuki, Y. H. Nakanishi and C. M. Pomerat. *Texas Reports on Biology and Medicine,* Vol. 18, pages 455-469, Fall 1960. (T.I.R.C. grantee: Pomerat)

Purpose of studies: In the course of *in vitro* development of most mammalian cell strains of both normal and malignant origin, chromosome numbers have been found to undergo changes from diploidy to a heteroploid state. Such transformations are associated with structural changes in addition to the numerical increase of chromosomes. Established cell strains invite quantitative studies on the effect of chemicals suspected of influencing the chromosomal complex. Accordingly, the work included attempts to develop epithelial lung strains with and without the presence of substances in tobacco smoke condensates. Such substances and benzpyrene were employed to determine whether the chromosomal configuration of an established lung strain could be altered.

Procedures: In the first study placental tissue from a healthy woman was obtained. The test objects used consisted of three types of amnion cell derivatives, because amnion cell strains are considered to be particularly useful for virological studies and may be affected by irradiation as well. The cell cultures were trypsinized and chromosomes were counted following a protracted series of sub-cultures.

In the second study lung tissues from a 2½ month male human fetus and from newborn to four-week-old kittens were used as test materials;

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explants were set up in culture bottles with the use of avian plasma clots, to which Eagle's medium with 10% horse serum was added. Two kinds of smoke condensates were used to test the cells, as was benzpyrene alone and benzpyrene in combination with a smoke condensate. The third study presents a more detailed account of the kitten lung experiments.

The fourth study was concerned with similar experiments with a cell strain from a C^3H male mouse carrying a subcutaneous tumor induced following injection of cigarette smoke condensates.

Findings: In the first study, the chromosome counts of human amnion cells obtained in freshly isolated elements before culture were 42, 48 and 55. The most frequent numbers in 25-day primary tissue culture preparations were 46 (25%) and 48 (21%). Counts made from cells of trypsinized cultures fixed on the 35th day of incubation (2nd sub-culture) had a range from 60 to 77 with a peak at 67. Cells in the 40th sub-culture (195 days from the initial trypsinization) showed a range from 58 to 90 with a peak at 66. In the latest observations in the 84th sub-culture (664 days) of a trypsinized culture of amnion tissue without embryonic extract the most frequent chromosome number was 75 (62%) in a narrower range of 69 to 78.

In the second study, two epithelial cell strains were established from the lung of the male fetus, one from cells in the presence of a cigarette smoke condensate (HL-S) and another from an untreated control (HL-C). At the outset, the most frequent chromosome numbers showed a shift to lower values in treated cultures, then a widened chromosome spectrum developed to a stage of "great spread" in both treated and control cultures. Finally, a narrow peak of heteroploids became established at 77 (HL-C) and 76 (HL-S).

The HL-C strain was challenged with two fractions of smoke condensate together with acetone and untreated controls, as well as with benzpyrene alone and with benzpyrene plus one of the smoke fractions. In the two controls in each changed environment the modal value was constantly at 77 for each observation from the 61st to the 81st sub-cultures (during 95 days). In contrast, the new modal value of 76 chromosomes was established after the appearance of dicentric chromosomes in some passages. It will be necessary to recheck whether pretreatment with the smoke condensate is significantly important in the establishment of a cell strain and whether the chromosomal changes are associated with malignant conversions.

In the third study, the most frequent chromosome number in the primary culture of kitten lung tissue was 38 (in 68% of the cells). With either the increasing numbers of sub-cultures or the period of cultivation, chromosome numbers showed a decrease of diploids and an increase of triploids or tetraploids. The latest observation on the chromosome numbers of the strain on the 411th day after the primary culture showed that the most frequent chromosome numbers were 90 (22%) and 92 (26%). Observation of mitotic activity of cells in the strain cultures by phase microscopy showed a rising proliferation index during the first seven days after inoculation.

In the fourth study the original mouse tumor was identified as a leiomyosarcoma, a tumor of the smooth muscle fibers containing imper-

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fectly differentiated embryonic cells. The induced tumors showed no invasion and spreading but grew under the skin, sometimes to a size larger than the host itself, without invasion. The most frequent chromosomal count from primary explants of this tumor was found to be 41 (42%) and hypotetraploid numbers ranged from 74 to 77 (24%). In 44% two number distributions were found, one in the diploid range (40-43) and the other in the tetraploid range (74-82), suggesting that the explants contained mixed cell lines. Following the 116th sub-culture the modal value for the chromosomes seemed to persist at 39, with a narrow range of distribution from 38 to 42. This modal value has remained without shift to date (63rd sub-culture). No evidence for the heteroploid transformation of chromosomes was observed.

In order to ascertain whether or not this mouse tumor strain was malignant, cells from several of the sub-cultures were inoculated into male C^3H mice. In four separate tests with varying procedures the results were negative three months or more after inoculation.

"EFFECT OF TOBACCO CONDENSATE ON RESPIRATORY TRACT OF WHITE PEKIN DUCKS." By R. H. Rigdon, M.D., Professor of Pathology, University of Texas Medical Branch, Galveston. *Archives of Pathology,* Vol. 69, pages 55-63, January 1960.

Purpose of study: In previous work the author investigated the mechanism of removal of fluid and particulate matter from the respiratory tract of white Pekin ducks, and found that liquid petrolatum and India ink entered the lungs and air sacs and remained there for varying periods of time. A study of the effects of tobacco condensate on the respiratory tract was undertaken in view of experimental studies by others of the effects of application of tobacco condensates and inhalation of cigarette smoke on various species of birds and mammals.

Procedure: Three ml. of cigarette smoke condensate were added to 19 ml. of liquid petrolatum, and one-half milliliter of this mixture was put into the trachea of young adult ducks once each day, except for holidays, for a maximum of 130 times. Histological studies of the tracheas from 99 normal ducks, 26 given petrolatum alone, and 26 given the tobacco condensate mixture, were made at varying intervals following treatment.

Findings: An acute and chronic reaction occurred in the trachea of a few of the birds instilled with the tobacco condensate mixture. A similar reaction, however, was present in normal birds and in some of those receiving only the petrolatum. Either the tobacco mixture was phagocytosed, or it passed between the epithelial cells lining the respiratory tract to reach the adjacent stroma, and subsequently it entered the lymphatic and blood vessels, normal channels of elimination of inhaled substances. There was nothing in this study to suggest neoplasia. An unexpected finding was the occurrence of amyloid-like material in the liver of three of nine ducks given the tobacco condensate for the longest periods — 130 injections in all. Amyloidosis has not been associated with cigarette smoking in any of the human statistical studies.

Other grantor: U.S. Public Health Service.

"THE EFFECT OF METHYLCHOLANTHRENE ON THE GASTRO-INTESTINAL TRACT OF THE DUCK." By R. H. Rigdon, M.D., Pro-

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fessor of Pathology, University of Texas Medical Branch, Galveston. *Texas Reports on Biology and Medicine,* Vol. 18, pages 275-283, Summer 1960.

Purpose of study: Past experiments have shown that variations in the occurrence of methylcholanthrene-induced tumors do occur in different tissues in a single host, that some researchers have produced tumors in an animal while others have not, and that there is need for an experimental approach to the problem of carcinogenesis in each host and in each tissue. This study was undertaken to determine the tumor response of ducks to the oral administration of methylcholanthrene.

Procedure: Twenty-one ducks aged 19 days were given 7.5 mg. of methlylcholanthrene suspended in 1 milliliter of liquid petrolatum daily for 30 days, at the rate of five each week. A second group of 13 ducks were given 30 mg. of methylcholanthrene crystals mixed with 270 mg. of flour in a gelatine capsule, at over-all rates which supplied 600 mg., 1200 mg. and 1800 mg. of methylcholanthrene respectively to three groups of birds. Birds died or were sacrificed from the 287th day on and the intestinal tracts were examined.

Findings: No tumors appeared in the gastro-intestinal tracts of any of the ducks. The methylcholanthrene crystals were shown to be rapidly excreted, and the absence of neoplasia may be explained by this failure of absorption of the carcinogen. The study emphasizes that neoplasms accepted on the basis of "association" with a carcinogenic agent always should be critically evaluated.

Other grantor: U.S. Public Health Service.

"OCCURRENCE AND ROLE OF GLYCOGEN IN THE EPITHELIUM OF THE ALVEOLAR MUCOSA AND OF THE ATTACHED GINGIVA." By Joseph P. Weinmann, Julia Meyer, Dorothy Mardfin and M. Weiss, Division of Oral Pathology, University of Illinois, College of Dentistry, Chicago, Illinois. *American Journal of Anatomy,* Vol. 104, pages 381-402, May 1959.

"DEGREE OF KERATINIZATION AND GLYCOGEN CONTENT IN THE UNINFLAMED AND INFLAMED GINGIVA AND ALVEOLAR MUCOSA." By M. D. Weiss, J. P. Weinmann, and J. Meyer. *Journal of Periodontology,* Vol. 30, pages 208-218, July 1959. (T.I.R.C. grantee: Dr. Isaac Schour)

Purpose of studies: Recent studies of the free gingiva have investigated the effects of inflammation on keratinization and glycogen deposition, and have stressed the fact that variable degrees of keratinization may occur in the same specimen in different parts of the free gingiva. These studies compare the different regions of the free gingiva, the attached gingiva, and the alveolar mucosa of uninflamed specimens with respect to degree of keratinization and content of glycogen, and reinvestigate the interrelations between inflammation, keratinization, and glycogen in these regions.

Procedures: Bilaterial biopsies of gingiva and alevolar mucosa were obtained from 52 men 27-70 years of age. Most of the men were cigarette smokers, some used other forms of tobacco, and a few were non-smokers. Glycogen was estimated using the periodic and acid-Schiff method controlled by diastase digestion; degrees of keratinization were determined

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using Bensley's specifications of Mallory's connective tissue stain; inflammation was evaluated from the density of inflammatory cell infiltration in the connective tissue underlying a given epithelial region; and cell size was estimated from the cell density established by cell counts.

Findings: In the absence of inflammation, the tendency for keratinization shows a regional gradient, being least marked in the crest region and most marked in the attached gingiva. Likewise, a regional gradient in incidence and concentration of glycogen was noted, the deposition being most marked at the crest and least marked in the attached gingiva. Study of inflamed regions showed that inflammation reduces the tendency for keratinization and increases the tendency for deposition of glycogen. The alveolar mucosa has a non-keratinizing epithelium and contains glycogen in all specimens. Keratinization and glycogen content are inversely related in uninflamed gingival regions, more markedly in inflamed gingival regions and most markedly in the alveolar mucosa. The glycogen deposits in the alveolar mucosa may have a structural function in maintaining the integrity of the cells.

Other grantor: U.S. Public Health Service.

II. *Human Lung Studies*

"PHYSIOLOGICAL RESEARCH IN CHRONIC PULMONARY DISEASE: AN EVALUATION OF ALVEOLAR AERATION, OXYGEN AND CARBON DIOXIDE TRANSFER AND THE PULMONARY CIRCULATION." By Hurley L. Motley, M.D., FCCP, Cardio-Respiratory Laboratory, University of Southern California School of Medicine, Los Angeles. *Diseases of the Chest,* Vol. 38, pages 250-260, September 1960.

Purpose of study: There is great need at the present time for further studies on the pulmonary circulation in chronic pulmonary disease. An adequate clinical evaluation of pulmonary function also requires measurements on the ventilatory status, and on the transfer of oxygen and carbon dioxide in the lungs. Single tests of lung function on a single aspect of the question are unsatisfactory. Important aspects of recent physiological research in chest medicine will be reviewed.

Procedure and findings: Measurements relating to alveolar aeration include spirograms of total, timed, mid-expiratory and maximal breathing capacity; residual air; intrapulmonary mixing; evaluation of bronchospasm; and special devices for air flow which measure the rapidity with which air can be exhaled from the lungs, among other variables. Significant information on air trapping is provided from the shape of the recorded spirogram tracing. The maximal breathing capacity provides significant information on the bellows action of the chest and lungs in addition to the timed vital capacity measurements. Bronchospasm is best evaluated before and after administration of a bronchodilator drug.

Residual air measurement and tests of intrapulmonary mixing are very important in the evaluation of lung function. In four years' experience with an improved helium closed circuit method more accurate results are obtained in severe emphysema cases than with the oxygen closed circuit, unless a nitrogen meter is used to monitor the nitrogen washout. Residual

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air has been a most sensitive test to detect changes in pulmonary status, but it may be correlated poorly with the chest roentgenogram.

The nitrogen washout on oxygen breathing is a most sensitive test for the evaluation of intrapulmonary mixing in the lungs, and reveals most graphically the presence of extensive obstruction in many of the smallest respiratory airways in asthma and emphysema. The curve of nitrogen exhalation with the single deep breath of oxygen and the nitrogen meter has not been found satisfactory in quantitative evaluation of intrepulmonary mixing. The nitrogen single deep breath test has been observed to improve after breathing an irritant such as cigarette smoke and to worsen after administration of a bronchodilator, just the reverse of the vital capacity measurements taken at the same time.

Valuable information has been derived from studies of the pressure volume relationship of the lung (compliance studies), which are best correlated clinically with total vital capacity. For satisfactory clinical evaluation, however, the compliance test does not appear to provide any more significant information than is obtained from the spirogram.

Adequacy of oxygen and carbon dioxide transfer is evaluated primarily from arterial blood oxygen saturation and carbon dioxide content at rest and with exercise. These and many other aspects of recent pulmonary research will serve to fill the need for accurate pulmonary function testing, for better diagnosis and treatment, and should be used along with the history, the physical and the roentgenological examination. The pulmonary physiologist must employ an adequate battery of tests well standardized and suitable for routine use under all health conditions, and the information so obtained in turn must be interpreted correctly as well as being dependable.

Other grantor: U.S. Public Health Service.

III. *Heart and Circulation*

"THE MYOCARDIAL METABOLISM OF FRUCTOSE." By William H. Danforth, M.D., Charles E. Hogancamp, M.D., Fred B. Ballard, M.D., and Richard J. Bing, M.D., Washington University School of Medicine, St. Louis, Mo. *American Journal of the Medical Sciences,* Vol. 238, pages 477-484, October 1959. (T.I.R.C. grantee: Bing*)

Purpose of study: In view of research which shows that the muscular substance of the heart has the ability to utilize a wide variety of foodstuffs, depending to a large extent on their availability, a study was undertaken to determine whether the myocardium extracts significant quantities of fructose and whether this carbohydrate affects the myocardial utilization of other substrates.

Procedures: Catheters were placed in the coronary sinuses of eleven human patients (two diabetics, three with mitral stenosis, one with aortic insufficiency, one with recent pericarditis, two with unexplained congestive heart failure, and two without detected heart disease) in a fasting state (before insulin administration to the diabetics). Arterial blood was obtained

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and coronary blood flow was determined. Arterial and coronary sinus samples for fructose, glucose, pyruvate, lactate, and ketones were obtained simultaneously, and the average of two consecutive blood samples measured. A priming dose of fructose, varying between 15 and 40 g., was administered, and intravenous infusion of 10% fructose in saline was maintained constantly. Sampling was carried out twice during the course of the infusion and the substrates were again measured.

Six anesthetized dogs were catheterized via the coronary sinus and the femoral artery, and also received 10% fructose in saline at a rate calculated to deliver 0.5 g. per kg. body weight in 30 minutes.

Findings: With initial arterial and coronary sinus levels of fructose at zero, arterial fructose levels rose slightly between the two samplings in four patients and fell in five of them, while arterial glucose rose in all patients, varying considerably from one to another. Blood pyruvate levels rose in the majority of patients, but not in the diabetics, and there was variation in other measurements.

Most of the dogs showed a slight positive myocardial fructose balance during the fructose infusion, and one showed a slight negative balance at the time of both samplings. In two dogs the coronary sinus concentration of fructose was greater than that in the artery five minutes after stopping infusion. Negative myocardial balances of fructose were detected in other animals 15 and 30 minutes after the onset of infusion.

It is possible that the variable results were due to movement of fructose in and out of the heart muscle as the result of changes in plasma concentration of this carbohydrate, but other factors such as variations in cardiac activity cannot be excluded. The results showed that myocardial utilization of glucose, pyruvate, lactate and ketone bodies were not noticeably affected by fructose in normals or diabetics.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, American Heart Association, and Burroughs, Wellcome and Co., Inc.

"METABOLIC CHANGES IN HEART MUSCLE DURING ANOXIA." By Gerhard Michal, Siegfried Naegle, William H. Danforth, Fred B. Ballard, and Richard J. Bing, Department of Medicine, Washington University School of Medicine, St. Louis, Mo. *American Journal of Physiology*, Vol. 197, pages 1147-1151, December 1959. (T.I.R.C. grantee: Bing)

Purpose of study: Studies of metabolism in the heart muscle following a period of anoxia have demonstrated impaired oxygen uptake if coronary perfusion is interrupted for more than two hours, and such hearts also produce significant amounts of lactic acid despite normal availability of oxygen. Hence it was decided to study changes in myocardial metabolism in greater detail during anoxia, particularly in respect of alterations in concentrations of glycogen, high energy phosphates and pyridine nucleotides following death of the test animal.

Procedure: Following anesthesia the chests of 12 mongrel dogs were opened, the pericardium incised, the aorta severed, and about half of the left ventricle removed. After a period of one half, one, or two hours, another specimen of the left ventricle was removed for analysis.

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Findings: Anoxia produced consistent changes in all substances studied. Diphosphopyridine nucleotide (DPN) decreased in all experiments; reduced diphosphopyridine nucleotide (DPNH) increased slightly, so that a drop in combined value occurred, particularly in the second hour. Glycogen stores in anoxic heart muscle disappeared rapidly and showed a progressive depletion after death. These studies illustrate that oxygen lack leads to rapid dephosphorylation of high energy phosphate compounds and to the subsequent formation of inorganic phosphorus.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, American Heart Association, and Burroughs, Wellcome and Co., Inc.

"MYOCARDIAL EXTRACTION OF Rb^{86} IN THE RABBIT." By Robert E. Mack, David D. Nolting, Charles E. Hogancamp, and Richard J. Bing, Department of Medicine, Washington University School of Medicine, St. Louis, Mo. *American Journal of Physiology,* Vol. 197, pages 1175-1177, December 1959. (T.I.R.C. Grantee: Bing)

Purpose of study: The isotope of Rubidium (Rb^{86}) is widely used in biological studies because of its similarity to potassium. The uptake of this cation by heart muscle suggested to other experimenters a method of quantitatively determining blood flow, but the present authors observed no apparent relationship between these two events in dog studies. Therefore, further evaluation of this factor was undertaken in rabbits.

Procedure: Perfusion was begun immediately after extraction on isolated rabbit hearts with warmed oxygenated rabbit blood containing traces of Rb^{86}. Cardiac contractions resumed promptly, and the outflow blood from the heart was collected, measured and the plasma concentration of Rb^{86} determined. Perfusion was continued for 20 minutes, permitting comparison of values for myocardial extraction at a wide variety of flow rates, both early and late in the experiment.

Findings: The mean value for myocardial extraction of Rb^{86} during the first ten minutes of infusion at all rates of flow was $43.3\% \pm 9.13$, a value similar to that observed by the authors in dog experiments (46%), which seemingly bore no relationship to either concentration or flow rate. However, the present investigation demonstrates a relationship not only between the myocardial extraction and the rate of flow, but also between the myocardial extraction and the length of time of flow, since extraction percentage was significantly lower during the later portion of perfusion at a wide variety of flow rates. It is conceivable that variability in myocardial or plasma electrolyte content in the experimental animals may be responsible for the wide range of extraction values determined.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, American Heart Association, and Hoffmann-LaRoche, Inc.

"MYOCARDIAL METABOLISM OF FATTY ACIDS." By Fred B. Ballard, William H. Danforth, Siegfried Naegle and Richard J. Bing, Departments of Medicine, Washington University and Wayne State University. *Journal of Clinical Investigation,* Vol. 39, pages 717-723, May 1960. (T.I.R.C. grantee: Bing)

Purpose of study: Recent research by other authors has shown that

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the principal lipid fraction of plasma concerned with the transport and metabolism of fatty acids is the nonesterified or free fatty acid (FFA) fraction, and that the heart uses a considerable amount of FFA. The present study was undertaken to determine further the role of fatty acids in myocardial metabolism.

Procedures: Coronary sinus and arterial blood samples were obtained simultaneously by catheter from human subjects and determination made of blood flow, glucose, total fatty acids (TFA), and FFA. The patients had hypertensive, rheumatic or arteriosclerotic heart disease but were not in congestive heart failure. Fasting individuals were tested and then given orally two ounces of a fat emulsion containing 19% saturated and 81% unsaturated fatty acids, and metabolic studies were carried out three or four hours later when little or no lipemia remained. After blood sampling from the initial studies, 10 mg. of aqueous heparin were given intravenously and repeat metabolic studies were conducted 20 minutes later.

Two sets of experiments were performed in dogs: myocardial utilization of fatty acids was determined in fasting dogs before and 20 minutes after heparin injection, while a second group was given Lipomul three hours before a similar cycle of determinations; in this group coronary blood flow was measured during lactescence and after clearing of the plasma with heparin.

Findings: The data on myocardial metabolism of fatty acids by fasting man and dog reveal that FFA average 6% of the mean arterial level of TFA in the human and about 3% in the dog. In the fasting human the mean myocardial extraction of FFA accounts for 42% of the TFA extraction and the esterified fraction makes up the balance; in the dog the FFA fraction accounts for only 23% of the total fatty acids extracted. The oxygen extraction ratios were 264% and 65% respectively, confirming other experiments which show that in the fasting state most of the energy in the heart is derived from fat metabolism.

Ingestion of a fat meal increased both plasma concentration and myocardial extraction of FFA. Heparin induced a fall in plasma concentration of TFA and an increase in concentration of FFA. The studies demonstrate that esterified fatty acids account for more than half of the total fats extracted by the myocardium. Myocardial extraction of FFA usually depends upon the arterial concentration of this fraction.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, and American Heart Association.

"EFFECT OF ISCHEMIA AND REOXYGENATION ON GLYCOLYTIC REACTION AND ADENOSINETRIPHOSPHATE IN HEART MUSCLE." By William H. Danforth, M.D., Siegfried Naegle, M.D. and R. J. Bing, M.D., Departments of Medicine, Washington University and Wayne State University. *Circulation Research,* Volume 8, pages 965-971, September 1960. (T.I.R.C. grantee: Bing)

Purpose of study: Previous work by the authors demonstrated that myocardial glycogen falls, while high energy phosphates and other compounds vary in either direction, during the first two hours of induced myocardial ischemia in dogs. This work is concerned with detailed changes in

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the glycolytic pathway of heart muscle during 15 minutes of anaerobiosis and when the ischemic heart is again perfused with oxygenated blood.

Procedure: Samples of myocardium from mongrel dogs were taken before removal of the heart and placed in an oxygen free saline bath. Saline was flushed through the left coronary bed through a sutured cannula to prevent formation of microthrombi, and a second sample of myocardium was taken after 15 minutes of anoxia. The coronary system was then perfused with well oxygenated blood and further samples obtained from a previously undamaged section of the left ventricle. The method of sampling might tend to bias the results, since parts of the myocardium distant from the large coronary vessels must be taken first, but this should not affect glycogen determinations. Several other related tests were made, including some with perfusion of blood directly from a donor dog.

Findings: During the 15 minute period of anoxia the fall in glycogen was as expected, and there was an increase in hexosemonophosphate (HMP) and in lactic acid. There was no accumulation of fructose 1, 6-diphosphate, dihydroxyacetone phosphate, or pyruvate. Adenosinetriphosphate (ATP) declined as expected. When the anoxic hearts were perfused, there was an initial adynamic phase (1 to 2 minutes) followed by fibrillation or irregular, ineffective ventricular contractions. Changes in myocardial glycogen concentrations were inconstant. Concentration of HMP declined rapidly to near normal levels at the end of five minutes. Concentration of ATP rose during the first two minutes; when KCl was added to the perfusion fluid, ATP concentration reached the initial level in 4 to 10 minutes; in experiments in which the heart was allowed to beat or to fibrillate, no consistent directional trend in ATP could be discerned after the first 2 minutes. Some aspect of the perfusion itself must be invoked to explain the decline in HMP with continued glycogenolysis.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, American Heart Association, Burroughs, Wellcome and Co., Inc., and Abbott Laboratories.

"POSSIBLE MECHANISM OF THE DECLINE IN MECHANICAL EFFICIENCY OF THE ISOLATED HEART." By K. Kako, J. D. Choudhury, and R. J. Bing, Department of Medicine, Wayne State University College of Medicine, Detroit, Mich. *Journal of Pharmacology and Experimental Therapeutics,* Vol. 130, pages 46-54, September 1960. (T.I.R.C. grantee: Bing)

Purpose of study: It is the purpose of this paper to describe experiments dealing with mechanisms of the decline in mechanical efficiency of the isolated heart and with the possible influence of liver and spleen in altering its mechanical efficiency.

Procedure: Coronary flow, glucose, lactate and ketone bodies were determined in closed chest dogs by catheters into the coronary sinus and the right ventricle and in isolated hearts by heart-lung preparation. In experiments in which liver and spleen were included in the perfusion circuit, these organs were quickly removed from a donor animal and immediately connected to the circuit of the heart-lung preparation, which had been operating for 45 minutes. Other experiments compared contractility of actomyosin bands from spontaneously failing and normal hearts.

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Findings: In the closed chest experiments oxygen and glucose usage fell significantly and lactate and ketone bodies also decreased. There was no significant change in the oxygen extraction ratio of glucose, lactate and ketone bodies of the isolated heart as compared to the heart *in situ*. The effect of the inclusion of the liver and spleen was a significant decline in myocardial oxygen consumption, but myocardial usages of glucose, lactate and ketone bodies were not affected; the oxygen extraction ratio of ketone bodies did rise, however. Contractility of actomyosin bands prepared from hearts failing in the heart-lung preparation was not impaired.

Cardiac output, left ventricular work, and myocardial efficiency declined significantly in all tests. Inclusion of liver and spleen in the perfusion circuit raised myocardial efficiency by lowering the oxygen usage of the heart. The heart rate declined. Addition of small quantities of norepinephrine and dopamine to the perfusion fluid increased myocardial efficiency without significantly altering heart rate. Following the onset of operation of the heart-lung preparation, the concentration of catecholamines in the perfusate gradually diminished. This trend could be partly reversed by inclusion of liver and spleen into the perfusion circuit.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, American Heart Association, Burroughs, Wellcome and Co., Inc., and Abbott Laboratories.

"IMPORTANCE OF CHEMICAL TRANSMISSION IN CARDIOLOGY AND NEUROPHARMACOLOGY." By Richard J. Bing, M.D., Wayne State University College of Medicine, Detroit, Mich. *Archives of Internal Medicine*, Vol. 104, pages 658-671, October 1959.

"THE HEART IN CONGESTIVE FAILURE." By Richard J. Bing, M.D., Wayne State University College of Medicine, Detroit, Mich. *Texas State Journal of Medicine*, Vol. 55, pages 931-936, December 1959.

"METABOLISM OF THE HEART IN FAILURE." By William H. Danforth, M.D., F. B. Ballard, M.D., K. Kako, M.D., J. D. Choudhury, M.D., and R. J. Bing, M.D., Department of Medicine, Washington University School of Medicine, St. Louis, Mo. *Circulation*, Vol. 21, pages 112-123, January 1960.

"PHYSIOLOGY OF THE MYOCARDIUM." By Richard J. Bing, M.D., Wayne State University College of Medicine, Detroit, Mich.; and William H. Danforth, M.D. and Fred B. Ballard, M.D., Washington University School of Medicine, St. Louis, Mo. *Journal of the American Medical Association*, Vol. 172, January 30, 1960, pages 438-444. (T.I.R.C. grantee: Bing)

These four studies are reviews of recent research by the authors and others contributing to knowledge of the heart in health and disease. The *first* paper stresses the equal importance of chemical transmitters such as acetylcholine and norepinephrine in both circulatory and neurophysiological events. The common denominator is the innervation of the heart and peripheral blood vessels by the autonomic nervous system. The physiological basis of excitation and inhibition of the central nervous system is thus recognized as a matter of unique interest to the cardiologist.

The most attractive aspect of the mutual antagonism or synergism of

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chemically related inhibitors is the mystery of this problem. For example, little is known of the relationship of norepinephrine to heart failure and to the intrinsic regulation of the coronary circulation. The tools available to investigate circulatory and neurophysiological relationships are still too crude to solve the problem.

In the *second* paper, it is noted that the role of the heart muscle in congestive failure probably has many facets, just as the clinical and dynamic features of heart failure vary with the type of disorder and the mode of its experimental production in animals. In general, however, myocardial failure occurs either acutely – which usually is observed experimentally in the heart-lung preparation — or chronically — as seen in clinical congestive heart failure.

There is some evidence that acute myocardial failure, whatever its origin, is accompanied by disturbances in the metabolism of the heart muscle. This disturbance in energy production conceivably may lead to diminished expulsive power of the heart and to progressive circulatory failure. Chronic myocardial failure is difficult to reproduce experimentally, on the other hand, and the results of dog studies may not be entirely applicable to man.

It is now possible to study heart metabolism by coronary sinus catheterization and thus to demonstrate that the myocardial usage of oxygen, glucose, pyruvate, lactate, fatty acids, amino acids, and ketones is not different in patients with congestive heart failure, in individuals with compensated heart disease, and in those without evidence of heart disease; values for the respiratory quotient are also identical in these groups. Since the mechanical work of the heart is usually decreased except in high output failure, the failing heart appears to be deficient in its ability to utilize energy for effective muscular contraction.

Further support for this conclusion has come from studies of contractile proteins (actomyosin) prepared from human hearts. The exact nature of disturbances in the contractile elements of the heart muscle is as yet uncertain, however, and the pathologist is unable to find specific changes in heart muscle of patients who died in congestive failure.

Since there are many factors which can lead to myocardial failure, it remains to be seen how disturbances in the heart muscle can be manifested in the general signs of heart failure, of which edema accompanied by sodium retention is the most important. One therefore must search for a connection relating the disturbances in the heart muscle with both the posterior pituitary and the renal tubules. Here, too, many factors have been shown to exist, and definitive knowledge is quite scanty concerning the direct stimulus to sodium rentention.

The *third* paper is particularly concerned with studies of the three phases of cardiac metabolism — energy production, energy conservation, and energy utilization — which show marked differences in the underlying mechanisms of heart failure. Thus, in failure with prolonged overload of the heart muscle, as occurs with hypertension, valvular heart disease and arteriosclerotic heart disease, an abnormality of energy utilization seems most likely. In other situations with heart failure, on the other hand, there appears to be a defect in energy production or conservation: in anemia, myocardial failure results in insufficient transport of oxygen for substrate

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metabolism, while in hyperthyroidism uncoupling of oxidative phosphorylation may lead to failure of energy conservation. In hemorrhagic shock and myocardial infarction, general or localized anoxia leads to defective energy production.

Spontaneous failure occurring in the heart-lung preparation is in all likelihood the result of diminished catecholamine and cholinergic substances of the perfusion fluid. It is apparent from this review that no common denominator exists as a cause of heart failure.

The *fourth* paper reviews advances in knowledge accomplished by studies of the heart at the molecular level. Anatomists are now studying its submicroscopic morphology, while physiologists and clinicians are exploring the electric activity of heart muscle cells and heart metabolism; biophysicists and pharmacologists also are making valuable contributions to the new approach to heart disease and its treatment.

The advent of catheterization of the coronary sinus has made it possible to study the use of various substrates by the human heart *in situ* and to observe the myocardial extraction of substrates and oxygen. Metabolic studies by this technique have demonstrated the importance of fatty acids in the nutrition of the myocardium. By the introduction of microelectrodes into the interior of single cells from the myocardium, the atrioventricular node, and the ventricular conducting system, it is now possible to follow electric changes and ionic fluxes in small units. This method has thrown new light on the significance of potassium and oxygen and the mechanism of fibrillation and pulsus alternans. Comparable advances have been made in the chemistry of myocardial proteins, the basic pharmacology of the heart, the pathological physiology of ischemia and anoxia, and the metabolism of the myocardium in congestive failure or after infarction.

Other grantors: U.S. Public Health Service, Life Insurance Medical Research Fund, American Heart Association, Burroughs, Wellcome and Co., Inc., and Abbott Laboratories.

"VASCULAR RESPONSES TO SMOKING TOBACCO COMPARED WITH RESPONSES TO SKIN TESTING OF TOBACCO EXTRACTS." By Kurt DeCrinis, M.D., Walter Redisch, M.D., FACP, Vincent Fontana, M.D., Arthur Lewis, M.D., Marion B. Sulzberger, M.D., FACP, and J. Murray Steele, M.D., New York University Medical Research Division, Goldwater Memorial Hospital, and Departments of Medicine and Dermatology, New York University College of Medicine, New York City. *Annals of Internal Medicine,* Vol. 52, pages 1935-1041, May 1960. (T.I.R.C. grantee: Sulzberger)

Purpose of study: It has been reported over the years that, in a certain percentage of subjects, smoking of tobacco causes vasoconstriction of peripheral vessels, as indicated by decrease in surface temperature and also by plethysmographically measured blood flow. The mechanism involved in this response has been the subject of some controversy. Likewise, discrepant views concerning the vascular beds involved in constrictor responses to tobacco smoking have been expressed. To gain further information in this area, it was decided to correlate vascular responses to tobacco with sensitivity responses in the skin.

Procedures: A group of 80 healthy smokers, including 27 females and

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53 males, aged 18 to 50 (average age 36), was tested before and after smoking a cigarette in six minutes under stable room temperature and humidity conditions, and after refraining from smoking or eating at least one hour before the test. Plethysmographic base line tracings, electrocardiograms, and ballistocardiograms were taken. The 80 subjects were also tested with intradermal injections of various tobacco extracts, and reactions were read after 10 minutes.

Findings: Of the total 80 healthy subjects, 38 (47.5%) revealed changes in at least one of the six circulatory measurements after tobacco smoking, while 42 (52.5%) showed no response. Only 10 subjects showed changes in the ballistocardiogram, and three in the electrocardiogram. Twenty-eight subjects (35%) showed a significant decrease in blood flow: 52 (65%) showed no change; none showed an increase. Surface temperature showed a decrease in only 11 subjects.

Of the 80 subjects, 32 (40%) showed a positive skin reaction to the tobacco extracts, and 48 (60%) remained negative. Of the 48 subjects with negative skin test, 43 revealed no significant change in measured peripheral blood flow after smoking; the remaining five subjects showed a significant decrease in blood flow. On the other hand, of the 32 subjects with positive skin test to tobacco, 21 (65.6%) showed a decrease in blood flow after smoking, while 11 showed no change.

These results suggest that a positive immediate wheal reaction to skin tests with tobacco extracts may indicate a subject's tendency to abnormal vascular responses, especially vascular constriction and decrease of peripheral blood flow, after cigarette smoking. The significance of the lack of correlation in the responses in surface temperature and in blood flow has to be ascertained through further work. The clue might well be that blood flow to the leg indicates predominantly muscle flow, while surface temperature is a function of skin flow only.

"CHOLESTEROL CHARACTERISTICS." By Caroline Bedell Thomas, M.D., Johns Hopkins University School of Medicine, Baltimore, Md. *Maryland State Medical Journal,* Vol. 8, pages 2-6, January 1959.

Points that are important to know in order to understand and interpret blood cholesterol levels in patients are as follows: First, the total serum cholesterol of healthy adults has a wide range of normal values. Second, the exact numerical value of cholesterol varies considerably with the particular laboratory technique employed, and should be judged within that framework. Third, there is little or no difference in the cholesterol level after eating as compared with that in the fasting state.

The fourth and fifth important factors are age and sex, which have quite a bearing on the cholesterol level. A sixth point is that despite measurable fluctuations, there is relative constancy of cholesterol levels over a period of weeks or months in a normal individual.

A seventh point has to do with the cholesterol of patients with coronary disease. It has been shown that these patients have higher mean cholesterol levels and that their levels fluctuate more widely than those of healthy persons of similar age. The question of whether these attributes *precede* the appearance of clinical disease becomes of immediate importance. Hypercholesterolemia occurs in persons in apparent good health. It appears

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that high cholesterol levels and coronary occlusion are closely associated and tend to run in families.

Additional studies are being made to determine, if possible, whether an association of higher cholesterol levels and smoking found in our students represents an inherited or constitutional difference rather than an effect of the smoking habit.

"COMPARISON OF SMOKERS AND NON-SMOKERS. I. A PRELIMINARY REPORT ON THE ABILITY TO TASTE PHENYLTHIOUREA (P.T.C.)." By Caroline Bedell Thomas and Bernice Hirschhorn Cohen, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md. *Bulletin of the Johns Hopkins Hospital,* Vol. 106, pages 205-214, April 1960.

Purpose of study: There is already some evidence pointing toward psychologic, physiologic and metabolic differences between certain groups of smokers and non-smokers. Demonstration of well established genetic differences would be even more conclusive, because such inborn traits are presumably stable and could not be the result of smoking. In order to explore the frequency of several genetic traits among groups of healthy smokers and non-smokers, it was decided to study the characteristics of blood donors at the Johns Hopkins Hospital, and to report preliminary findings on the ability to taste phenylthiourea (P.T.C.), a compound that is an experimentally valuable aid in testing taste levels.

Procedures: Taste tests, using filter paper impregnated with P.T.C., were carried out on 597 white and 232 Negro male donors at the Johns Hopkins Hospital Blood Bank. Each donor was interviewed as to his smoking habits. The subject was asked whether or not he tasted anything, and if so, what the taste was like. He was then grouped according to ability to taste P.T.C.

Findings: Among both white and Negro donors, significant differences in ability to taste P.T.C. were found between smokers and non-smokers. Among white male donors, heavy cigarette smokers showed a strikingly higher proportion of tasters than did non-smokers (65.9% versus 42.7%). Former smokers, occasional smokers and light smokers closely resembled the non-smokers as to proportion of tasters. The significant findings were unrelated to age.

"CHARACTERISTICS OF SMOKERS COMPARED WITH NON-SMOKERS IN A POPULATION OF HEALTHY YOUNG ADULTS, INCLUDING OBSERVATIONS ON FAMILY HISTORY, BLOOD PRESSURE, HEART RATE, BODY WEIGHT, CHOLESTEROL AND CERTAIN PSYCHOLOGIC TRAITS." By Caroline Bedell Thomas, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md. *Annals of Internal Medicine,* Vol. 53, pages 697-718, October 1960.

Purpose of study: Reports that smokers, especially heavy smokers, have a higher mortality rate from coronary heart disease than do non-smokers make it important to determine whether those who smoke are fundamentally different from those who do not, or whether they are essentially alike. If alike, they may be considered as a single population with a

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uniform life expectancy, but if smokers have constitutional differences from non-smokers, the two groups might have different mortality rates, and one group could not serve as a control for the other in statistical studies. It was decided to study the smoking habits and other characteristics of 10 successive classes of medical students in detail.

Procedures: Detailed information was obtained from 597 men and 60 women concerning smoking habits, family history, measurements of blood pressure, heart rate, height, weight, and cholesterol level, as well as results of a cold pressor test, a double Master exercise test, a ballistocardiographic smoking test, and a Rorschach test. All subjects were in good health and free from clinical evidence of hypertension and coronary heart disease.

Findings: Significant differences recorded showed: (1) The smokers, as a group, more often gave a history of parental hypertension; had higher mean values for heart rate and pulse pressure; higher cholesterol levels; comprised a larger proportion of heavy individuals; and more often reported anger and an urge to eat when under stress. (2) Non-smokers, as a group, had higher mean values for diastolic pressure; more often reported decreased activity under stress; and more often gave a high number of white space response in the Rorschach test. (3) A parallelism existed between the presence or absence of factors thought to indicate high susceptibility to hypertension and/or coronary disease, on the one hand, and the presence or absence of the habit of smoking, on the other. (4) Broad areas of similarity were found in the responses to the cold pressor, Master and ballistocardiographic smoking tests; in academic excellence; and in most of the Rorschach variables. (5) The differences observed in the parental histories indicate that smokers and non-smokers have a somewhat different heritage, and suggest that at least some of the variations found in individual traits may be genetic in origin.

Other grantor: U.S. Public Health Service.

"EFFECTS OF ERGOMETRINE (ERGONOVINE) ON THE ISOLATED ATHEROSCLEROTIC HEART OF THE CHOLESTEROL-FED RABBIT." By Dorothy Karp, Seymour H. Rinzler, and Janet Travell, Department of Pharmacology, Cornell University Medical College, New York, New York. *British Journal of Pharmacology,* Vol. 15, pages 333-344, June 1960. (T.I.R.C. grantee: Travell)

Purpose of study: Intravenous injections of ergometrine (U.S.P. ergonovine) produce a transient S-T segment depression in the electrocardiogram that is characteristic of coronary insufficiency in patients with coronary artery disease. Like changes are induced in rabbits with experimental coronary atherosclerosis. These changes do not occur in man or test animal with a normal coronary circulation. In the absence of data, it seemed important to study the effects of this drug directly on the coronary circulation.

Procedure: Two groups of male Dutch rabbits were started at the same time either on a stock diet or on a similar diet with addition of 2% cholesterol. Serial ergometrine tests were done after 6 to 8 weeks on the diets and thereafter usually at weekly intervals until the test became positive. Control electrocardiograms were taken before, and 5 and 10

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minutes after pentobarbitone injection. Ergometrine maleate 0.05 mg./kg. was injected intravenously and electrocardiograms on two leads repeated after 1, 3, 5, 7 and 10 min. or longer, depending on the duration of effect. One or two days after the ergometrine test became positive, the atherosclerotic heart was isolated and the coronary circulation perfused; control rabbits were treated similarly. After perfusion the heart was fixed in formalin and sections taken for pathological study.

Findings: A total of 29 atherosclerotic hearts of cholesterol-fed, ergometrine-positive rabbits and 32 normal hearts of ergometrine-negative control rabbits were perfused with various drugs. Most of the ergometrine-positive hearts (96%) showed advanced intimal atherosclerosis of the small intramural arteries; one heart showed a less advanced change. The larger arteries seldom showed such changes. No changes were seen in the control hearts. Initially coronary flow, heart rate and amplitude of contraction differed in normal and atherosclerotic hearts. With respect to ergometrine, coronary flow was the only parameter to show a significant difference in the response of the normal and atherosclerotic heart to medium doses of this drug, but the changes observed with smaller and larger doses were not statistically significant. The difference in the flow response of the normal and atherosclerotic heart to ergometrine was striking during the wearing off of a vasopressin-induced reduction in coronary flow.

In contrast to the reproducible effects of a given dose of ergometrine, vasopressin induced tachyphylaxis in the isolated heart. Furthermore, the effects of vasopressin were essentially similar for normal and atherosclerotic isolated rabbit hearts. These observations suggest fundamental differences in the mechanism of action of these two drugs on the heart. One may speculate that the effects of ergometrine on coronary flow are mediated at least in part through mobilization of catecholamines, whereas vasopressin acts more directly on receptors. When catecholamines are depleted during atherogenesis, a direct action of ergometrine on receptors may be unmasked.

Other grantors: U.S. Public Health Service and Josiah Macy, Jr. Foundation.

"LIPID INFILTRATION IN THE RABBIT IRIS." by Duane G. Wenzel, James A. Turner and Donald Kissil, School of Pharmacy, University of Kansas, and the Veterans Administration Hospital, Kansas City, Missouri. *American Journal of Ophthalmology,* Volume 48, pages 535-537, October 1959. (T.I.R.C. grantee: Wenzel)

Purpose of study: Although lipid infiltration of the sclera and cornea of the rabbit and human has been reported, similar effects have been unnoticed in the iris. This is the first to report observation of lipid infiltration in the iris from cholesterol and cottonseed oil administration in the diet of experimental animals.

Procedures: Nicotine was given for 24 hours in the drinking water of some groups of animals in quantities to correspond to the use of various amounts of tobacco by humans, with appropriate controls. The eyes were subjected to gross and microscopic study.

Findings: There were no obvious differences between the eyes of animals receiving cholesterol alone as a dietary additive and those also receiving

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nicotine. Microscopically, the iris was virtually completely infiltrated with fat-filled macrophages. Similar depositions including large vacuoles of fatty material were found in the ciliary body. Sections through the posterior sclera revealed the fatty material to be deposited in all layers of the wall.

IV. *Psycho-physiological*

"MASCULINITY AND SMOKING." By Carl C. Seltzer, Peabody Museum, Harvard University, Cambridge, Mass. *Science,* Vol. 130, pages 1706-1707, December 18, 1959.

Purpose of study: In order to obtain a fuller understanding of the apparent relationship of heavy smoking to lung cancer and coronary disease, it was pertinent to inquire into the nature of the individuals who practice the smoking habit – their personality, physiology, and biogenetic characteristics. This report deals with one aspect of the somatic biogenetic material – namely, the body build of these men as related to their smoking habits.

Procedure: The basic data on which the analysis was based were derived from a follow-up study of 252 Harvard sophomores first seen between 1938 and 1942, who were selected for their lack of visible abnormality. In the course of the physical anthropological examination of the subjects while still sophomores, each individual was rated with respect to a body-build complex described as the "masculine component," which refers to the element of masculinity in the individual as indicated by his external morphological features. The more the pattern of anatomical traits tends toward the extreme masculine form, the stronger is the masculine component; the greater the departure from the extreme masculine type towards the more feminine build, the weaker is the masculine component in the individual.

Findings: Weakness of the masculine component was significantly more frequent in smokers than in non-smokers, and significantly more frequent in heavier smokers than in non-smokers and moderate smokers combined. The increased frequency of the degree of weakness of the masculine component was consistent and progressive, and the heavier smokers showed the greatest proportion of individuals with "weak" or "very weak" masculine components. These data suggest that for a specified type of individual, smoking may be a reflection of certain personality and behavioral traits which are characteristic of his biological make-up.

V. *Tobacco Chemistry*

"THE EFFECT OF INDOLE-3-ACETIC ACID ON FORMALDEHYDE METABOLISM." By Clifford S. Sato, Kerckhoff Laboratories of Biology, California Institute of Technology, Pasadena. *Journal of Biological Chemistry,* Vol. 235, pages 2087-2091, July 1960. (T.I.R.C. grantee: Dr. James Bonner)

Purpose of study: Plant tissues readily incorporate the methyl group of L-methionine into the methyl ester of pectic substances, influenced by the

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hormonal action of indole-3-acetic acid, but formaldehyde appears to be a still more effective methyl precursor in plants. The present investigation was undertaken to determine: (a) the effect of formaldehyde upon the growth rate of the oat coleoptile, (b) the rate of formaldehyde incorporation into cell wall components as well as into other cellular fractions, and (c) the influence of indoleacetate upon such incorporation.

Procedure: Coleoptile sections were cut below the tip of oat seedlings grown for 96 hours in vermiculite, previously soaked in distilled water, and were floated on unbuffered aqueous solution of formaldehyde-C^{14}. A series of duplicated experiments were conducted for incubation periods ranging up to 240 minutes, each representing a different day and a fresh batch of seedlings. Radioactivity was determined.

Findings: Formaldehyde was incorporated most rapidly into substances soluble in 80% ethanol. Substantial activity also appears in the cell wall fraction. It is of interest that formaldehyde incorporation into pectin increases with time. Indole-3-acetic acid promotes the incorporation of the labeled compound into pectin and, at a lag of one hour, into residual pectin, and also depresses the incorporation of formaldehyde-C^{14} into nitrogenous compounds.

"INSECTICIDE RESIDUES ON TOBACCO." By T. G. Bowery, W. R. Evans, F. E. Guthrie and R. L. Rabb, Departments of Chemistry and Entomology, North Carolina State College, Raleigh. *Agricultural and Food Chemistry*, Vol. 7, pages 693-702, October 1959. (T.I.R.C. grantee: Bowery)

Purpose of study: Information has been lacking on the magnitude and fate of insecticide residues on tobacco, although a few partial studies have been reported since the advent of organic insecticides in tobacco culture. The major pesticides used on flue-cured tobacco are TDE and endrin, which are usually applied more frequently and closer in time to harvesting than other pesticides, therefore constituting a greater potential hazard.

Procedures: Fifty or more leaves of green and flue-cured tobacco, 50-leaf samples of flue-cured tobacco from commercial auction markets, and five-pack samples of commercial cigarettes were taken for analyzing. Total organic chlorine content as well as TDE and endrin contents were measured by sensitive laboratory methods.

Findings: Rather high levels of TDE and endrin residues may occur on green tobacco at priming. There is approximately a 40% loss of these residues during flue-curing, but the residues tend to go slightly subsurface and little or no additional loss occurs during commercial processing. Dilution of the pesticide residues by blending with other tobaccos and additives during commercial cigarette manufacture reduces the level of these insecticides in cigarettes. Appreciable dissipation occurs during smoking, but small and detectable amounts of TDE are still found in the mainstream smoke of commercial cigarettes. Studies on the fate of endrin residues in cigarette smoke and on the site, level and fate of the insecticide-derived inhalation products in mammals are in progress.

Other grantors: Southern Regional Research Project S-22 and Shell Chemical Corporation.

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"STUDIES OF THE BIOGENESIS OF THE RING SYSTEMS OF NICOTINE." By Thomas Griffith, Kenneth P. Hellman and Richard L. Byerrum, Kedzie Chemical Laboratory, Michigan State University, East Lansing. *Journal of Biological Chemistry,* Vol. 235, pages 800-804, March 1960. (T.I.R.C. grantee: Byerrum)

Purpose of study: Other researchers have shown that the pyridine ring of nicotinic acid is utilized to form the pyridine ring of nicotine in sterile cultures of tobacco root, but data are inadequate on other possible intermediates in the biosynthesis of the ring systems of nicotine. Therefore an investigation was made of the incorporation of several C^{14} labeled compounds, which might be interconvertible with acetate in metabolism, into nicotine in intact tobacco plants.

Procedure: Tobacco plants were grown for two to three months in a greenhouse, and after removal of the roots were placed in an inorganic nutrient solution to allow new roots to develop. Radioactive nicotine was synthesized from plants fed hydroponically with labeled acetates, propionates and glycerol, and was degraded to obtain carbon 2 of the pyrrolidine ring as barium carbonate. When propionate-2-C^{14} was fed, carbon 2 of the pyrrolidine ring contained 12% of the labeled carbon and 42% was associated with carbons 3, 4 and 5. When glycerol-1,3-C^{14} was administered, 6% of the C^{14} was associated with carbon 2 and 27% with carbons 3, 4 and 5.

Findings: If the assumption is made that a symmetrical intermediate is formed during the incorporation of the labeled precursors into the pyrrolidine ring, an equal quantity of C^{14} would be associated with carbons 2 and 5, and this pattern would be consistent with the postulate that both propionate and glycerol entered the tricarboxylic acid cycle and were converted to glutamate during the synthesis of the pyrrolidine ring of nicotine. The pyridine ring of nicotine from the propionate-fed plants contained 39% of the C^{14} and 57% of the labeled carbon when glycerol was the precursor. If all the glycerol was metabolized to acetate during its incorporation into nicotine, only 40% of the original C^{14} would be expected to reside in the pyridine ring. Therefore, glycerol must have been utilized for pyridine ring synthesis by a metabolic pathway that excludes acetate.

"METABOLISM OF NICOTINE IN THE HUMAN AND EXCRETION OF PYRIDINE COMPOUNDS BY SMOKERS." By Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr., Department of Pharmacology, Medical College of Virginia, Richmond. *Journal of Pharmacology and Experimental Therapeutics,* Vol. 127, pages 92-95, October 1959 (T.I.R.C. grantee: Dr. P. S. Larson)

Purpose of study: It has been observed frequently that only a small fraction of the nicotine absorbed in the smoking of tobacco is excreted by the human, and animal experimentation shows this to be the probable result of active metabolism and not storage or elimination by other pathways. This work was undertaken to describe studies on the isolation of some of the metabolites of nicotine present in the urine of the human non-smoker and of pyridine compounds present in the urine of human smokers.

Procedures: A normal adult male non-smoker received an oral dose of 30 mg. of *l*-nicotine daily for three days in consecutive hourly doses of 3

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mg. each in gelatine capsules, and metabolites were exhaustively extracted and identified by standard procedures. Urine of smokers (60 l.) was obtained from laboratory workers and extracted by the same methods.

Findings: During the 3-day period the non-smoker excreted about 10% of the administered nicotine in the form of cotinine. Since the smokers' urine was collected only during the daytime and without data on respective smoking habits, the percentage of metabolism could not be calculated. Chromatographic evidence pointed to the presence of cotinine, desmethylcotinine and hydroxycotinine in all the samples examined. It is inferred, as indicated in dog studies, that the pathway of nicotine metabolism in the human may be nicotine → cotinine → hydroxycotinine plus desmethylcotinine.

Other grantors: U.S. Public Health Service and The American Tobacco Company.

"DEMETHYLATION OF COTININE *IN VIVO*." By Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman, and Einosuke Wada. *Journal of the American Chemical Society,* Vol. 81, pages 3951-3954, August 5, 1959.

"THE ISOLATION AND STRUCTURE OF A KETOAMIDE FORMED IN THE METABOLISM OF NICOTINE." By Herbert McKennis, Jr., Edward R. Bowman, and Lennox B. Turnbull. *Journal of the American Chemical Society,* Vol. 82, pages 3974-3976, August 15, 1960. (T.I.R.C. grantee: Dr. P. S. Larson)

Purpose of studies: The metabolism of (-)-nicotine in mammals leads to the excretion of (-)-cotinine and a variety of components not found in the controls. These papers represent further research into the identity and metabolic roles of these substances.

Procedures: In the earlier study, attention was focused solely on the isolation of chloroform-soluble metabolites of nicotine and cotinine in dogs. In the second study, separation in crystalline form of a chloroform soluble amphoteric metabolite was undertaken.

Findings: The isolation of (-)-desmethylcotinine and hydroxycotinine as a result of the metabolism of cotinine in the first study affirmed the importance of the role attributed to cotinine as an intermediate in nicotine metabolism. It was also apparent that many new metabolic pathways for the degradation of cotinine must be considered. As a result of this and previous studies by these authors, seven metabolic components have been separated which represent about 30% of the total metabolites of nicotine. Hence, the metabolism of nicotine in humans and laboratory animals presents a diversity and complexity far in excess of original estimates.

In the second study the isolation of gamma-(3-pyridyl)-beta-oxo-N-methylbutyramide as a result of administration of (-)-cotinine to dogs further enlarged the known role of cotinine as an intermediate in nicotine metabolism.

Other grantors: U.S. Public Health Service and The American Tobacco Company.

"THE OXIDATION OF NICOTINE. I. KINETICS OF THE LIQUID PHASE REACTION NEAR ROOM TEMPERATURE." By Robert H.

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Linnell, Department of Chemistry, University of Vermont, Burlington. *Tobacco Science,* Vol. 4, pages 89-91, April 29, 1960.

Purpose of study: Although the chemical degradation and oxidation of nicotine have been investigated extensively, the kinetics of the reaction of oxygen with nicotine has not previously been reported.

Procedure: Nicotine was vacuum distilled, and tested fresh or after storage for various periods under N_2. To obtain kinetic data an apparatus was constructed with a reaction flask mounted on a shaker which had variable amplitude and speed. Rates of O_2 uptake are strongly decreased on exposure of the nicotine to air or oxygen.

Findings: The kinetic data from 15°-40° C. gave an over-all activation energy of 6.8 kcal. An increasing infrared band at 5.9 microns indicates cotinine is one of the products. These experiments provided strong evidence of the free-radical nature of the oxidation of nicotine, which follows the general mechanism of olefin oxidation, and a nicotine hydroperoxide may be expected as an intermediate. Further work is under way to isolate the proposed hydroperoxide and to provide more details on the mechanism of the reaction.

"ARSENIC CONTENT OF COMMERCIAL TOBACCO, 1917-1958." By F. E. Guthrie, C. B. McCants and H. G. Small Jr., Departments of Entomology and Soils, North Carolina State College, Raleigh. *Tobacco Science,* Vol. 3, pages 20-22, May 8, 1959. (T.I.R.C. grantee: McCants)

Purpose of study: Scattered and conflicting data on the arsenic content of tobacco have appeared from time to time since it was first reported in 1927. Since 1952 arsenic compounds have been removed from the list of recommended insecticides, and strenuous efforts have been made to reduce the use of these materials on tobacco. In view of the interest in this subject, cigarettes and tobacco samples produced during the period 1917-1958 were obtained for analysis, to determine their arsenic content.

Procedures: Tobacco samples were obtained from the following sources: 1917, 1931, 1935, 1951 — commercial brands of cigarettes; 1953 through 1957 — composite samples of tobacco from various U.S. areas; 1957 — three popular brands purchased in February; 1958 — six popular brands purchased in April and an additional eleven purchased in December, including regular, King size, filter, and menthol cigarettes. The As_2O_3 content of the tobacco was determined by standard procedures.

Findings: The data show an increase in arsenic in cigarettes from 1917 (12.8 to 17.5 ppm) to 1951 (51.0 to 56.5 ppm), with a sharp decrease thereafter: (8.5 to 12.3 ppm in 1957, 5.3 to 14.4 in April 1958, and 2.7 to 6.5 in December 1958). The cigarette data correspond closely to arsenic values found in unmanufactured flue-cured tobaccos for 1953-57. The evidence here is that the arsenic content of present-day American cigarettes is within the range of 3 to 12 ppm, with an average of about 6 ppm.

"THE BACTERIAL OXIDATION OF NICOTINE. III. THE ISOLATION AND IDENTIFICATION OF 6-HYDROXYPSEUDOOXYNICOTINE." By Lawrence I. Hochstein and Sydney C. Rittenberg, Department of Bacteriology, University of Southern California, Los Angeles. *Journal of Biological Chemistry,* Vol. 235, pages 795-799, March 1960. (T.I.R.C. grantee: Rittenberg)

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Purpose of study: Previous studies by the authors have established that an enzyme fraction obtained from a nicotine-oxidizing bacterium catalyzes the oxidation of nicotine and 6-hydroxynicotine. This work was undertaken to identify the product of such oxidation.

Procedure: Cell-free extracts were prepared of a gram-negative bacterium isolated from soil and grown in a medium containing nicotine and other compounds. Ultraviolet spectrophotometry, paper chromatography, optical rotation and other determinations were performed as described in previous papers. 6-Hydroxynicotine (6-OHN) was isolated from growth medium, and that portion of the crude bacterial extract which precipitated at 40 to 60% saturation with respect to ammonium sulfate (the 40-60 fraction) was shown to oxidize 6-OHN in the absence of methylene blue, although such extract will catalyze the aerobic oxidation of nicotine only in the presence of the dye. Other tests indicated that the compounds formed by the crude extract, at the expense of nicotine, and by the 40-60 fraction, at the expense of 6-OHN, were identical. Identification of the oxidation product was undertaken.

Findings: The product isolated has been identified as 6-hydroxypseudooxynicotine on the basis of elemental analysis, UV absorption spectra, and similarity to such a compound obtained by other methods. The compound has been obtained from oxidation by resting cells, crude extracts, and an ammonium sulfate fractionated extract of the nicotine-oxidizing bacterium. The metabolic evidence shows this compound to be the second oxidative product in the bacterial metabolism of nicotine.

"IDENTIFICATION OF ESCULETIN IN TOBACCO AND IN CIGARETTE SMOKE." By L. J. Dieterman, C. H. Yang, Y. Nakagawa, and S. H. Wender, Department of Chemistry, University of Oklahoma, Norman. *Journal of Organic Chemistry*, Vol. 24, pages 1134-1136, August 1959. "IDENTIFICATION OF CAFFEIC ACID IN CIGARETTE SMOKE." By Chao-Hwa Yang, Y. Nakagawa, and S. H. Wender. *Journal of Organic Chemistry*, Vol. 25, pages 658-660, April 1960. (T.I.R.C. grantee: Wender)

Purpose of studies: In the purification of scopoletin from cigarette smoke and from various tobacco extracts, two or more interfering blue fluorescing compounds persisted with the scopoletin through several paper chromatographic developments. The purpose of these studies was to identify these interfering compounds.

Procedures: In the first study, separation, purification and identification was carried out in leaves and flowers from greenhouse tobacco plants, in leaves from Burley, Turkish and flue-cured tobacco, and in the mainstream smoke from eight brands of cigarettes. In the second study the smoke from eight brands of cigarettes as well as the tobacco from 120 cigarettes of one brand were utilized.

Findings: Esculetin (6,7-dihydroxycoumarin) was identified for the first time in the first study in the flowers and leaves of the greenhouse plants and in flue-cured and air-cured tobacco leaf samples. The mainstream smoke of the cigarettes contained only a trace amount of esculetin. In the second study, caffeic acid was identified in cigarette smoke for the first

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time reported by any investigator, although previously reported by others in various cured tobaccos. Each of the eight cigarette brands tested was found to contain free caffeic acid in the mainstream smoke.

Other grantors: U.S. Public Health Service and Atomic Energy Commission.

VI. *Other Studies*

"EFFECT OF NICOTINE AND TOBACCO ON MUSCLE FUNCTION." By Ernst Fischer, M.D., Herbert Silvette, Ph.D., P. S. Larson, Ph.D., and H. B. Haag, M.D., Medical College of Virginia, Richmond. *American Journal of Physical Medicine,* Vol. 39, pages 63-77, April 1960. (T.I.R.C. grantee: Haag)

The effect of nicotine and tobacco on skeletal muscle has received far less attention in the literature than either the practical importance of the neuromuscular system or the scientific interest that nicotine action on muscle deserves. A review of observations on the subject shows that the direct effect of nicotine on motor functions is due to its action on the nervous system, upon the muscles themselves, or to simultaneous effect upon both.

Subject headings reviewed here are nicotine action upon the cerebrum and the thalamus, on the spinal cord, on somatic peripheral nerves and on sensory nerve endings, direct action on skeletal muscle, the effect of denervation on nicotine's action on muscle, the exact site of its skeletal muscle action, and the importance of the paralytic phase of muscular action in acute nicotine poisoning, all of which relate to animal experimentation; in the realm of human studies, the review discusses the effect of smoking on human muscular efficiency and clinical conditions affecting muscle function.

Investigation has shown that human muscular efficiency is very much more influenced by psychological than by physiological factors. The once widely-held belief that intermittent claudication can be directly caused by the misuse of tobacco is now declining, and it is becoming increasingly recognized that this condition is but a symptom of chronic occlusive arterial disease, although there is strong clinical opinion that tobacco, in certain instances, may influence the natural course of peripheral arterial disease.

However, the acute vasoconstrictor effect of smoking is mainly evident in the skin circulation, and any nicotine effect from smoking upon the muscular circulation must be regarded as doubtful. Muscle cramps are a symptom of many different pathological conditions, but vascular disorders are no longer regarded as of etiological importance. It has been reported that tremor is one of the neuromuscular disturbances which may occur in chronic tobacco poisoning, but it would appear that, so far as the ordinary smoker is concerned, there is little or no untoward effect of the habit on skeletal muscle function.

"MEASUREMENT OF TOBACCO SMOKING." By P. S. Larson, Ph.D., H. B. Haag, M.D., and H. Silvette, Ph.D., Medical College of Virginia, Richmond. *Medical Times,* Vol. 88, pages 417-429, April 1960. (T.I.R.C. grantee: Haag)

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A comprehensive review of medical literature dealing with the subject shows that, almost invariably, the smoking habits of patients in clinical and epidemiological studies are described in terms of daily consumption of cigarettes or tobacco in other forms. The results bear a very indeterminate and perhaps undeterminable relationship to the *effective dosage* to which the patient is subjected.

If a patient is asked how many cigarettes he smokes daily, his answer — even if he can actually remember — is meaningless unless we know precisely how much of these cigarettes is "burned into the mouth," and then how much of that portion of the smoke is actually deposited on susceptible tissues and/or absorbed into the blood stream. The manner of smoking (for example, with or without inhalation), the duration of smoking, the rate of smoking, the portion of a cigarette consumed, and other variables exist.

In addition to these uncertainties, there are virtually no consistent and comparable methods of rating smoking habits in the literature. The meaning of adjectives such as "light," "moderate," "heavy" and "excessive" varies considerably with each writer; many studies convert pipe smoking and cigar usage into cigarette "equivalents," and even the criteria of "non-smoking" vary from author to author.

All of the factors entering into "effective dosage" can be reasonably well estimated, given the time and trouble, but there is another factor of perhaps even greater importance: the patient's constitutional or genetic make-up, which is so far largely undeterminable except by its ultimate influence or effect. Moreover, a multitude of writers over very many years have insisted upon recognition of the fact that men vary in their sensitivity or susceptibility to tobacco. A quantitative yardstick applied to one smoker is not necessarily valid for another.

"TOBACCO AND RENAL FUNCTION AND DISEASES OF THE URINARY TRACT. A REVIEW OF THE EFFECTS OF SMOKING AND NICOTINE ADMINISTRATION IN MAN AND ANIMALS." By P. S. Larson, Ph.D., H. B. Haag, M.D., and H. Silvette, Ph.D., Medical College of Virginia, Richmond. *Virginia Medical Monthly*, Vol. 87, pages 332-341, June 1960. (T.I.R.C. grantee: Haag)

A survey of the world literature on tobacco has failed to discover any previous comprehensive review of the effects of smoking on renal function or the relationship of tobacco to diseases of the urinary tract. It has pointed up also the relative paucity of observations of the effects of nicotine on renal and urinary-tract function in experimental animals. This review may serve the double purpose of indicating what is known, and what it would be desirable to know. It comprises the following eleven subject headings:

Effect of tobacco on the mechanisms of renal secretion in animals; effect of nicotine on the composition of urine; histopathology of the kidney in acute and chronic poisoning; effect of tobacco on water balance; effect of nicotine on the ureter and urinary bladder; effects of smoking and nicotine on renal function in man; effect of smoking and nicotine on the composition of human urine; nicotine tests for neuro-hypophyseal function; smoking and diseases of the urinary tract; therapeutic uses of tobacco

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as a diuretic and in diseases of the urinary tract; and effect of smoking on water exchange in man.

This survey has revealed a curious and even a unique phenomenon: on the one hand, quite massive doses of nicotine have surprisingly little direct effect on kidney function and structure in animals; and the extensive literature on acute tobacco or nicotine poisoning in man confirms the absence of "acute" effects of tobacco use on this system, and "chronic" effects are equally conspicuous by their absence.

On the other hand, the effect of tobacco smoking in releasing antidiuretic hormone from the posterior lobe of the pituitary gland represents one of the relatively few predictable and reproducible pharmacological actions of *ordinary* smoking on the human organism, a fact of great and interesting importance. The role of the hypothalamus as a center for integration of visceral function has come to be appreciated only in recent years, and it is hoped that future research will be directed towards the elucidation of the central rather than the peripheral autonomic effects of smoking and/or nicotine. It is possible to speculate that the well-known alterations in appetite and body weight which follow smoking and stopping smoking are similarly mediated through the hunger and satiety centers which have been shown to exist in the hypothalamus.

"TOBACCO AMBLYOPIA. THE EVOLUTION AND NATURAL HISTORY OF A 'TOBACCOGENIC' DISEASE." By H. Silvette, H. B. Haag, and P. S. Larson, Department of Pharmacology, Medical College of Virginia, Richmond. *American Journal of Ophthalmology*, Vol. 50, pages 71-100, July 1960. (T.I.R.C. grantee: Haag)

The history of so-called "tobacco amblyopia," first described in 1792, illustrates the birth, growth, and senescence of a disorder which, it seems, may at best have been largely illusory. An extensive examination of the literature provides an object lesson which the physician may wish to keep in mind when the question of tobacco etiology is raised in other diseases as fashionable now as tobacco amblyopia once was.

Assuming that the incidence of a disease has apparently gone down while exposure to its presumed etiologic agent has significantly risen, several possible explanations suggest themselves. The most obvious is that the presumed relationship is not causative. There is also the possibility that the organism has developed in time some resistance to the causative agent, whether hereditarily determined or as a result of external factors (for example, better general health and nutrition). Genetically determined changes in resistance may be ruled out, since one century is less than a moment in human evolution. Nor can one avoid the suspicion (now unprovable) that many of the earlier reported cases had been falsely diagnosed.

Fortunately the great mass of published material on tobacco amblyopia contains within itself sufficient inconsistencies and contradictions to enable one to cancel out a good deal of it.

The key question is posed: "Why should only a few people who smoke get this amblyopia?" Whatever the answer to this crucial question, it is difficult to believe that tobacco or tobacco smoking comprises any significant part of it.

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Titles of Previously Published Abstracts

Following are titles of abstracts that appeared in the previous Reports:

I. *Cancer Research*

"TISSUE SPECIFICITY OF SERUM COMPONENTS." By S. D. YEH, M.D., W. F. SEIP, B.S., C. BURCH, A.B., and F. W. BARNES JR., M.D., with the aid of R. RUTHERFORD, M.D., Departments of Medicine and Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Md. *Archives of Internal Medicine*, Volume 103, pages 933-948, June 1959. (T.I.R.C. grantee: Barnes)

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"A CONSTANT-RATE INFUSION APPARATUS." By QUENTIN S. MCKENNIS, EDWARD R. BOWMAN, and HERBERT MCKENNIS, JR. *Toxicology and Applied Pharmacology*, Vol. 1, pages 61-64, January 1959. (T.I.R.C. grantee: Dr. P. S. Larson)

"THE BACTERIAL OXIDATION OF NICOTINE. I. NICOTINE OXIDATION BY CELL-FREE PREPARATIONS. II. THE ISOLATION OF THE FIRST OXIDATIVE PRODUCT AND ITS IDENTIFICATION AS (1)-6-HYDROXYNICOTINE." by L. I. HOCHSTEIN and SYDNEY C. RITTENBERG, Department of Bacteriology, University of Southern California, Los Angeles. *Journal of Biological Chemistry*, Vol. 234, pages 151-155 and 156-160, January 1959. (T.I.R.C. grantee: Rittenberg)

"THE DARK FIXATION OF CO_2 BY SUCCULENT LEAVES: METABOLIC CHANGES SUBSEQUENT TO INITIAL FIXATION." By PAUL SALTMAN, VICTORIA H. LYNCH, GEORGE M. KUNITAKE, CLYDE STITT and HERBERT SPOLTER, Department of Bio-chemistry and Nutrition, School of Medicine, University of Southern California, Los Angeles. *Plant Physiology*, Vol. 32, No. 3, pages 197-200, May 1957.

"DARK FIXATION OF CO_2 BY SUCCULENT LEAVES: CONSERVATION OF THE DARK FIXED CO_2 UNDER DIURNAL CONDITIONS." By GEORGE KUNITAKE and PAUL SALTMAN. *Plant Physiology*, Vol. 33, pages 400-403, November 1958.

"DARK FIXATION OF CO_2 BY TOBACCO LEAVES." By GEORGE KUNITAKE, CLYDE STITT, and PAUL SALTMAN. *Plant Physiology*, Vol. 34, pages 123-127, March 1959. (T.I.R.C. grantee: Saltman)

"IDENTIFICATION OF SCOPOLETIN IN CIGARETTE TOBACCO AND SMOKE." By CHAO-HWA YANG, YASUSHI NAKAGAWA, and SIMON H. WENDER, Department of Chemistry, University of Oklahoma, Norman. *Journal of Organic Chemistry*, Vol. 23, No. 2, pages 204-205, February 1958.

"FORMATION OF SCOPOLETIN FROM ESCULIN AND ESCULETIN IN THE RAT." By CHAO-HWA YANG, H. D. BRAYMER, P. L. PETRAKIS, M. R. SHETLAR, and S. H. WENDER. *Archives of Biochemistry and Biophysics*, Vol. 75, No. 2, pages 538-539, June 1958.

"SCOPOLETIN IN COMMERCIAL TOBACCO PRODUCTS." By CHAO-HWA YANG, YASUSHI NAKAGAWA, and SIMON H. WENDER. *Tobacco Science*, Vol. 2, pages 111-114. August 29, 1958.

"QUANTITATIVE STUDIES OF SCOPOLETIN IN CIGARETTE SMOKE AND TOBACCO." By CHAO-HWA YANG, YASUSHI NAKAGAWA, and SIMON WENDER. *Analytical Chemistry*, Vol. 31, pages 2041-2044, December 1958. (T.I.R.C. grantee: Wender)

VII. *Other Studies*

"IMMUNOLOGICAL ASPECTS OF TOBACCO AND SMOKING." By H. SILVETTE, PH.D., P. S. LARSON, PH.D., and H. B. HAAG, M.D., Department of Pharmacology, Medical College of Virginia, Richmond. *American Journal of Medical Sciences*, Vol. 234, No. 5, pages 561-589, November 1957.

"MEDICAL USES OF TOBACCO, PAST AND PRESENT." By H. SILVETTE, PH.D., P. S. LARSON, PH.D., and H. B. HAAG, M.D. *Virginia Medical Monthly*, Vol. 85, pages 472-484, September 1958. (T.I.R.C. grantee: Haag)

"CANCER OF THE LUNG – THE SEX RATIO. A REVIEW OF THE PROBLEM." By HELEN KIRCHOFF and R. H. RIGDON, Department of Pathology, University of Texas Medical Branch, Galveston. *Texas Reports on Biology and Medicine*, Vol. 17, pages 29-48, Spring 1959. (T.I.R.C. grantee: Rigdon)

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Recipients of Grants

Following is a list of all recipients of grants approved by the Scientific Advisory Board since initial grants were made in late 1954. It should be noted that some of the projects have been completed.

GRANTEE AND INSTITUTION	PROJECT TITLE *("C" indicates project completed; "P" indicates a report on work has been published)*
CLARENCE M. AGRESS, M.D., *Chief, Cardiovascular Laboratory,* Veterans Administration Center, Los Angeles 25, California	The Measurement of the Functional Status of the Human Heart by Frequency Spectrum Analysis of its Vibrational Energy
D. MURRAY ANGEVINE, M.D., *Professor of Pathology,* University of Wisconsin Medical School, Madison, Wisconsin	Pathologic—Anatomic Study of Cellular Changes in Human Bronchi (C)
FREDERICK W. BARNES, JR., M.D., PH.D., *Associate Professor of Medicine and Physiological Chemistry,* Johns Hopkins University School of Medicine, Baltimore 5, Maryland	The Role of Hyperplasia in Tissue Response to Chronic Damage (C—P)
RALPH S. BECKER, PH.D., *Associate Professor of Chemistry,* University of Houston, Houston, Texas	An Investigation of the Spectral and Chromatographic Characteristics of Aromatic Hydrocarbons
SAMUEL BELLET, M.D., *Director, Division of Cardiology,* Philadelphia General Hospital, Philadelphia, Pennsylvania	The Effect of Nicotine on Cardiac Irritability in the Presence of Reserpine, and the Effect of Nicotine on Coronary Blood Flow of Dogs with Coronary Insufficiency (C—P)
RICHARD J. BING, M.D., *Professor of Medicine and Chairman, Department of Medicine,* Wayne State University College of Medicine, Detroit 7, Michigan (formerly Professor of Medicine, Washington University School of Medicine, St. Louis, Missouri, and Professor of Experimental Medicine and Clinical Physiology, The Medical College of Alabama, Birmingham)	The Effect of Smoking on the Coronary Blood Flow and Certain Phases of Myocardial Metabolism in Patients with Arteriosclerotic or Hypertensive Cardiovascular Disease (P) Studies in Cellular Physiology of Heart Muscle (P) Measurement of Coronary Blood Flow by Means of Radioactivated Albumin The Effect of Smoking on Coronary Blood Flow in Patients with Arteriosclerotic Heart Disease and the Effect of Nicotine on Storage of Amines in Heart Muscle
FRED G. BOCK, M.S., PH.D., *Senior Cancer Research Scientist,* Health Research Inc., Roswell Park Division, Buffalo, New York (see Moore)	Investigation of the Biological Effects of Cigarette Smoke (C—P)
JAMES F. BONNER, PH.D., *Professor of Biology,* California Institute of Technology, Pasadena, California	Enzymatic Study of Methylation Reactions in Plant Tissue (C—P)

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GRANTEE AND INSTITUTION	PROJECT TITLE
TOM G. BOWERY, PH.D., *Pesticide Residue Laboratory, Chemistry Department,* North Carolina State College, Raleigh, North Carolina	TDE and Endrin Residues in Cigarette Smoke (C—P)
JOSEF BROZEK, PH.D., *Professor and Chairman, Department of Psychology;* Lehigh University, Bethlehem, Pennsylvania (formerly Professor, Laboratory of Physiological Hygiene, University of Minnesota School of Public Health, Minneapolis)	Biological Characteristics of Men and Their Smoking Habits (C—P)
E. M. BUTT, M.D., *Professor of Pathology,* University of Southern California School of Medicine; *Chief Pathologist,* Los Angeles County Hospital, Los Angeles 33, California	Pathologic—Anatomic Study of Cellular Changes in Human Bronchi (C) Study of Trace Metal Storage of Pulmonary and Liver Tissue by Spectographic and Chemical Methods (C)
RICHARD U. BYERRUM, PH.D., *Professor of Chemistry,* Michigan State University, East Lansing, Michigan	Biosynthesis of the Pyridine Ring of Nicotine (P)
SISTER M. EMILY CAHILL, PH.D., *Chairman, Chemistry Department,* Regis College, Weston, Massachusetts	Comparison of Analytical Methods by Determining the Percent Recovery of Arsenic Added at Known Levels to Tobacco Samples and a Broad Survey of the Amount of Arsenic Present in Tobacco Samples from a Wide Variety of Sources
WILLIAM H. CARNES, M.D., *Professor of Pathology,* University of Utah College of Medicine, Salt Lake City, Utah	Pathologic—Anatomic Study of Cellular Changes in Human Bronchi (C)
LEOPOLD CERECEDO, PH.D., *Professor of Biochemistry and Nutrition,* University of Puerto Rico, School of Medicine, San Juan, Puerto Rico, (formerly Professor of Biochemistry, Fordham University, New York, N. Y.)	A Study of Early Chemical Changes in the Lungs of Tumor-Bearing Rats and Mice (C—P)
HANS T. CLARKE, D.SC., *Professor of Biochemistry,* Columbia University College of Physicians and Surgeons, New York, N. Y. (see Gottschall)	Proteolytic Activities of the White Blood Cells of Men and the Effect on White Blood Cell Activities of Carcinogens, Nutrition and Other Influences (C)
JULIUS H. COMROE JR., M.D., *Director, Cardiovascular Research Institute,* University of California Medical Center, San Francisco, California	The Effect of Smoking Upon Airway Resistance (C—P) Analysis of Case Histories on Emphysema
DEAN M. CONNORS, M.D., *Associate Director, Department of Laboratory Medicine,* St. Mary's Hospital, Madison 5, Wisconsin	A Study of the Alterations in the Human Bronchial Wall Occurring with Aging, with Particular Emphasis on Elastic Tissue Changes and Associated Changes in the Bronchial Lumen Size

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GRANTEE AND INSTITUTION	PROJECT TITLE
PHILIP COOPER, M.D., *Chief, Surgical Service,* Veterans Administration Hospital, Bronx, New York; *Clinical Professor of Surgery,* Albert Einstein Medical College, Bronx (formerly Professor of Clinical Surgery, Boston University School of Medicine; Chief, Surgical Service, and Director, Surgical Research Laboratory, Veterans Administration Hospital, Providence, Rhode Island)	A Study of the Effects of Cigarette Smoking on Levels of Gastric Acid, Pepsin and Uropepsin (C—P) A Study of the Effect of Extracts of Tobacco on Cultures of Tumor and Normal Cells. Animal Transplants of Tumor Tissue from Tissue Cultures
ALBERT DAMON, M.D., PH.D., *Assistant Professor of Medical Anthropology, Department of Industrial Hygiene,* Harvard School of Public Health, Boston, Massachusetts	Body Form, Smoking, and Alcohol Consumption Among Italian-American Men
R. F. DAWSON, PH.D., *Professor of Botany,* Columbia University, New York, N. Y.	An Investigation of the Metabolism of Pyridine Compounds in the Tobacco Plant (P)
ANDREW S. DIBNER, PH.D., *Executive, Psycho-Research,* The Age Center of New England, Inc., Boston, Massachusetts (see Whiskin)	Psychological and Behavioral Characteristics of Inhalers Among Smokers
EDWARD F. DOMINO, M.D., *Assistant Professor of Pharmacology,* University of Michigan, Ann Arbor, Michigan	Effects of Tobacco Smoke and Nicotine on the Central Nervous System
JOHN W. ECKSTEIN, M.D., *Assistant Professor of Internal Medicine,* College of Medicine, State University of Iowa, Iowa City, Iowa	Responses of the Peripheral Veins in Man to the Intravenous Administration of Nicotine (P) Foot Blood Flow Responses to Smoking in the Presence of Hyperlipemia and Hypertension
HANS E. FALK, PH.D., *Senior Research Associate, Department of Pathology,* University of Southern California School of Medicine, Los Angeles, California	Examination of Cigarette Paper and Cigarette Smoke Condensates for Aromatic Polycyclic Hydrocarbons (C) A Compilation of Fluorescence Spectra of Polycyclic Aromatic Hydrocarbons and Closely Related Compounds Which Are of Interest in the Study of Air Pollutants, and Cigarette Smoke in Relation to Lung Cancer Etiology (C—P) The Effects of Tobacco Smoke Condensate on the Defense Mechanisms of the Rat in Detoxification of Polycyclic Aromatic Hydrocarbons and the Competitive Inhibition Between the Polycyclic Hydrocarbons in Condensate with Regard to Carcinogenesis
DANA L. FARNSWORTH, M.D., *Henry K. Oliver Professor of Hygiene and Director of University Health Services,* Harvard University, Cambridge 38, Massachusetts (see Heath and McArthur)	Personality and Smoking in College Graduates: A Fifteen-Year Follow-up Study (C)

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GRANTEE AND INSTITUTION	PROJECT TITLE
FRANK C. FERGUSON, JR., M.D., *Chairman, Department of Pharmacology,* Albany Medical College, Albany 8, New York	Effects of Tobacco Smoke Upon the Function of the Cardiovascular System in Animals and Man (C)
RUSSELL S. FISHER, M.D., *Chief Medical Examiner,* State of Maryland; *Professor of Legal Medicine,* University of Maryland Medical School, Baltimore, Maryland	Pathologic—Anatomic Study of Cellular Changes in Human Bronchi (C)
B. L. FREEDLANDER, M.D., *Director of Cancer Research,* Mount Zion Hospital and Medical Center, San Francisco 15, California (see French)	Experiments on the Possible Carcinogenic and Cocarcinogenic Action of Tobacco Products (P)
FREDERICK A. FRENCH, A.B., *Research Associate,* Mount Zion Hospital and Medical Center, San Francisco, California (see Freedlander)	Carcinogenicity, Cocarcinogenicity and Anti-carcinogenicity of Dietary Factors in Relation to Pulmonary Tumors. Possible Interrelationship of Tobacco Bases and Dietary Factors. Chemical Studies on Pyridine Bases Including Niacin Analogs
JACK FREUND, M.D., *Assistant Professor of Pharmacology,* Medical College of Virginia, Richmond 19, Virginia	Correlation of Multi-technical Procedures Performed on the Peripheral Circulation of Normal Individuals in Recumbent and Erect Positions and After Exercise Before and After Sham and Actual Smoking (C)
	A Study of the Effects of Cigarette Smoking on the Peripheral Circulation of Individuals with Arteriosclerosis Obliterans and Other Peripheral Vascular Diseases, Utilizing Multi-technical Procedures
GEORGE O. GEY, M.D., *Director, Finney-Howell Cancer Research Laboratory, Department of Surgery,* Johns Hopkins Hospital, Baltimore, Maryland	Fellowships for Studying the Culture of Human Lung Tissue and the Effects of Known and Possible Carcinogenic Agents Upon Such Tissue
GERTRUDE Y. GOTTSCHALL, PH.D., *Assistant Professor of Biochemistry, Department of Pathology and Microbiology,* The Rockefeller Institute for Medical Research, New York 21, N. Y. (see Clarke)	Proteolytic Activities of the White Blood Cells of Man and the Effect on White Blood Cell Activities of Carcinogens, Nutrition and Other Influences (C)
A. CLARK GRIFFIN, PH.D., *Head of Biochemistry Department,* M.D. Anderson Hospital and Tumor Institute, University of Texas Medical Center, Houston 25, Texas	The Effect of Exposure to Cigarette Smoke on the Induction of Cancer by Chemical Compounds (C—P)
MORTON I. GROSSMAN, PH.D., M.D., *Associate Clinical Professor of Medicine,* University of California Medical Center, Los Angeles 24, California	The Effect of Smoking on Certain Gastric Functions

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GRANTEE AND INSTITUTION	PROJECT TITLE
CARL C. GRUHZIT, PH.D., M.D., *Associate in Physiology and Pharmacology*, University of Pennsylvania Graduate School of Medicine, Philadelphia 4, Pennsylvania (now Lecturer in Physiology, University of Hong Kong)	Pharmacologic Study of Nicotine and Related Alkaloids (C)
H. B. HAAG, M.D., *Professor of Pharmacology*, Medical College of Virginia, Richmond 19, Virginia	Preparation for Publication of a Book on the Biologic Aspects of Tobacco and its Smoke (C—P)
JOSEPH H. HAFKENSCHIEL, M.D., *Director, Cardiopulmonary Unit*, Lankenau Hospital, Philadelphia 31, Pennsylvania	Measurement of Coronary Blood Flow, Cardiac Work and Cardiac Oxygen and Carbohydrate Metabolism in Normotensive Subjects Before and After Intravenous Nicotine and After Smoking Standard Cigarettes (C—P)
RICHARD J. HAVEL, M.D., *Assistant Professor of Medicine*, University of California Medical School, San Francisco, California	A Study of the Effects of Smoking and Nicotine Administration on Sympathoadrenal Function and Fatty Acid Metabolism
HERBERT R. HAWTHORNE, M.D., *Chairman, Department of Surgery*, University of Pennsylvania Graduate School of Medicine, Philadelphia 4, Pennsylvania	Attempts to Induce Pulmonary Neoplasms in Experimental Animals by Exposure of the Tracheo-Bronchial System to Tobacco Smoke (C)
CLARK W. HEATH, M.D., *Professor of Medicine and Director of Health Services*, Tufts University, Medford, Massachusetts (formerly at Harvard University, Cambridge, Massachusetts) (see Farnsworth and McArthur)	Personality and Smoking in College Graduates: A Fifteen-Year Follow-up Study (C—P)
PAULINE HEIZER, PH.D., *Research Associate in Cytology and Cytochemistry*, San Francisco Institute of Medical Sciences, San Francisco 15, California (see Richards)	A Comparative Study of Early Histological and DNA Changes in the Epidermis of Two Strains of Mice (C57 Blacks and Swiss Websters) After Daily Applications of Whole Cigarette Smoke Condensate (Alone and Combined with Croton Oil) and the Carcinogens 20-Methylcholanthrene and 3,4-Benzpyrene
LAWRENCE L. HESTER, JR., M.D., *Professor and Chairman, Department of Obstetrics and Gynecology*, Medical College of South Carolina, Charleston, South Carolina	The Relationship of the Use of Tobacco Products to the Outcome of Pregnancy
[illegible] CURTIS HOFF, PH.D., M.D., *Professor and Chairman, Department of Neurological Science*, Medical College of Virginia, Richmond 19, Virginia	Cerebral Autonomic Changes Produced by Tobacco Smoke, Nicotine or Cotinine, a Metabolite of Nicotine
RUSSELL L. HOLMAN, M.D., *Professor and Head, Department of Pathology*, Louisiana State University School of Medicine, New Orleans 12, Louisiana (deceased, see McGill)	Pathologic—Anatomic Study of Cellular Changes in Human Bronchi (C)
	The Influence of Tobacco Smoking on Acute Myocardial Infarction

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GRANTEE AND INSTITUTION	PROJECT TITLE
F. HOMBURGER, M.D., *President*, Bio-Research Institute, Inc., Cambridge, Massachusetts	Studies on Carcinogenesis and the Bioassay of Carcinogenic Agents (P) Comparative Studies of Effects of Various Tobacco Smoke Condensates on Skins of Mice
JERRY HART JACOBSON, M.D., *Director of Electrophysiology*, New York Eye and Ear Infirmary, New York 3, N. Y.	A Comparison of Electroretinography as a Means of Evaluating the Effect of Vasoconstrictor Drugs Upon Cerebral and Retinal Circulation With Other Techniques for This Determination (C)
JULIUS H. JACOBSON II, M.D., *Associate Professor of Surgery and Director of Surgical Research*, College of Medicine, University of Vermont, Burlington, Vermont	Lung Homotransplantation
ANDREW A. KANDUTSCH, PH.D., *Staff Scientist*, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine	To Determine to What Extent Tobacco 'Tar' Mimics the Action of Carcinogenic Hydrocarbons in the Skin and Other Tissues (C)
ANCEL KEYS, PH.D., *Professor of Physiological Hygiene and Director, Laboratory of Physiological Hygiene*, University of Minesota School of Public Health, Minneapolis 4, Minnesota	Characteristics of Men, Including Smoking, in Populations Differing in the Incidence of Coronary Heart Disease (C—P)
JOSEPH B. KIRSNER, M.D., *Professor of Medicine*, University of Chicago School of Medicine, Chicago, Illinois	The Effect of Tobacco Smoking Upon Basal Gastric Secretions in Man (C)
KENNETH P. KNUDTSON, M.D., *Assistant Chief, Laboratory Service*, Veterans Administration Hospital, Seattle, Washington; *Professor of Pathology*, University of Washington Medical School, Seattle, Washington	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi (C)
ALVIN I. KOSAK, PH.D., *Associate Professor of Chemistry*, Washington Square College, New York University, New York 16, N. Y.	The Isolation and Identification of Certain Lower-Boiling Components of Cigarette Smoke (C)
MARVIN KUSCHNER, M.D., *Professor of Pathology*, New York University College of Medicine; *Director of Pathology*, Bellevue Hospital, New York 16, N. Y.	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi (C)
THOMAS C. LAIPPLY, M.D., *Associate Professor of Pathology*, Northwestern University Medical School, Chicago, Illinois	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi (C)
PAUL S. LARSON, PH.D., *Professor of Pharmacology*, Medical College of Virginia, Richmond 19, Virginia	Enzymatic Transformations of Nicotine and Related Compounds (P) The Possible Effect of Tobacco Smoke and Nicotine on Ascorbic Acid Metabolism

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GRANTEE AND INSTITUTION	PROJECT TITLE
GUSTAVE A. LAURENZI, M.D., *Assistant Professor of Medicine,* Seton Hall College of Medicine, Jersey City 4, New Jersey	Studies in Bronchitis: A Correlated Investigation of: (a) The Effect of Smoking on the Bacteriology of the Respiratory Tract of Humans, and (b) The Effect of Cigarette Smoke and Sulfur Dioxide (Air Pollutant) on the Clearing of Bacteria from the Respiratory Tracts of Small Animals (Mice, Rats)
CECILIE LEUCHTENBERGER, PH.D., *Senior Biologist and Cytochemist,* Children's Cancer Research Foundation, Boston, Massachusetts (formerly Associate Professor of Cytology, Western Reserve University School of Medicine, Cleveland, Ohio)	A Correlated Histological, Cytological and Cytochemical Study of the Tracheo-Bronchial Tree from Mice Exposed to Cigarette Smoke (P)
ROBERT H. LINNELL, PH.D., *Associate Professor of Chemistry,* University of Vermont, Burlington, Vermont	The Oxidation of Nicotine by Gaseous Oxygen: Mechanism, Products and Kinetics (C—P) The Autoxidation of Nicotine
DAVID E. MANN, JR., PH.D., *Associate Professor of Pharmacology,* Temple University School of Pharmacy, Philadelphia 40, Pennsylvania	Effect of Tobacco Smoke and Tobacco Residues on Methylcholanthrene-Induced Skin Carcinogenesis in Mice (C)
CHRISTOPHER M. MARTIN, M.D., *Assistant Professor of Medicine and Director, Division of Infectious Diseases,* Seton Hall College of Medicine, Jersey City 4, New Jersey	Possible Interactions of Viruses and Substances in Tobacco Smoke Condensate
CHARLES C. McARTHUR, PH.D., *Psychologist to the University Health Services,* Harvard University, Cambridge 38, Masachusetts (see Heath and Farnsworth)	Social and Personal Determinants of Smoking Behavior (C—P) The Social Mediation of Smoking Behavior
CHARLES B. McCANTS, PH.D., *Associate Professor of Soils,* School of Agriculture, North Carolina State College, Raleigh, North Carolina	Arsenic Content of Soils and Absorption by the Tobacco Plant (C—P)
HENRY C. McGILL, JR., M.D., *Acting Head, Department of Pathology,* Louisiana State University School of Medicine, New Orleans 12, Louisiana (see Holman)	The Effects of Environmental Factors on Development of Atherosclerosis as Revealed by Autopsy of Accident Victims
FORDE A McIVER, M.D., *Assistant Professor of Pathology,* Medical College of South Carolina, Charleston, South Carolina	Environmental Factors and Pulmonary Disease. I. Asbestos Dust
KELLY T. McKEE, M.D., *Associate Professor of Medicine,* Medical College of South Carolina, Charleston, South Carolina	Study of Lung Function in Smokers and Non-Smokers (C—P)
VICTOR A. McKUSICK, M.D., *Associate Professor of Epidemiology and Chief, Division of Medical Genetics,* Johns Hopkins University School of Medicine, Baltimore 5, Maryland	A Combined Genetic, Physiologic, Clinical and Epidemiologic Study of Buerger's Disease

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GRANTEE AND INSTITUTION	PROJECT TITLE
JAMES G. MILLER, M.D., PH.D., *Professor of Psychiatry and Psychology, and Director, Mental Health Research Institute*, University of Michigan, Ann Arbor, Michigan	The Behavioral Effects of Smoking Under Stress (C)
HUGH MONTGOMERY, M.D., *Associate Professor of Medicine*, University of Pennsylvania Medical School, Philadelphia 4, Pennsylvania	Influence of Tobacco Smoking on the Blood Flow of Skin and of Muscles of Extremities in Sympathectomized and Unsympathectomized Subjects (C) Influence of Nicotine (i.v.) and Tobacco Smoking on Blood Flow in Human Skin and Skeletal Muscle (P)
P. O'B. MONTGOMERY, JR., M.D., *Associate Professor of Pathology*, University of Texas, Southwestern Medical School, Dallas 35, Texas	Investigation of the Role of the Nucleolus in the Normal and the Malignant Cell
GEORGE E. MOORE, PH.D., M.D., *Director*, Roswell Park Memorial Institute, Buffalo 3, New York (see Bock)	An Investigation of the Physiological Effects of Direct Inhalation of Tobacco Smoke by Laboratory Animals and the Study of the Biological Response of Laboratory Animals to Continuous Ingestion of Diet-Tobacco Product Mixtures (C)
HURLEY LEE MOTLEY, M.D., *Professor of Medicine and Director, Cardio-Respiratory Laboratory*, University of Southern California School of Medicine, Los Angeles 17, California	A Study of the Effects of Smoking on Pulmonary Function (C—P)
WILLIAM S. MURRAY, SC.D., *Research Associate and Administration Director*, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine	The Production of Genetically Controlled Animals and Tumors for Use in Experimental Research on Tobacco in Relation to Health by (a) the Expansion of Known Inbred Stocks and Sources of Tumor Supply; (b) the Production of Such Hybrids or Heterozygous Types as Become Necessary; and (c) the Relation of this Material to Specific Experimental Work at the Laboratory (C)
DONALD M. PACE, PH.D., *Professor of Physiology and Director, Institute for Cellular Research*, University of Nebraska, Lincoln, Nebraska	Fellowships for Training in Tissue Culture Techniques (C) Study of the Effects of Tobacco Smoke Constituents on Various Strains of Tissue Cells Cultivated *In Vitro* (P)
EDWARD W. PELIKAN, M.D., *Associate Professor of Pharmacology and Experimental Therapeutics*, Boston University School of Medicine, Boston, Massachusetts	A Study of Structure-Activity Relationships Among Drugs Which Affect Nicotine-Sensitive Physiological Mechanisms (P)
OTAKAR J. POLLAK, M.D., PH.D., *Executive Director*, Dover Medical Research Center, Inc., Dover, Delaware	Possible Effect of Tobacco Derivatives on Arterial and Myocardial Tissue Cultures

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GRANTEE AND INSTITUTION	PROJECT TITLE
C. M. POMERAT, PH.D., *Director of Biological Research,* Pasadena Foundation for Medical Research, Pasadena, California (formerly Professor of Cytology, University of Texas Medical Branch, Galveston)	Fellowships for Studying the Culture of Human Lung Tissue and the Effects of Known and Possible Carcinogenic Agents Upon Such Tissue (P)
H. R. PRATT-THOMAS, M.D., *Dean and Professor of Pathology,* Medical College of South Carolina, Charleston, South Carolina	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi (C—P) Application of a New Bio-Assay Technique in Examination of Cigarette Smoke Condensates for Possible Carcinogens (C—P) Carcinogenesis in the Laboratory Animal: A Comparison of Species Response to Standardized Sites of Application
HOBART A. REIMANN, M.D., *Professor of Medicine,* Hahnemann Medical College and Hospital, Philadelphia 2, Pennsylvania	The Possible Effect of Tobacco or Nicotine in Periodic Disorders, a Newly-Recognized Syndrome
VICTOR RICHARDS, M.D., *Professor of Surgery and Executive Head, Department of Surgery,* Stanford University School of Medicine, San Francisco 15, California (see Heizer)	A Comparative Study of the Effects of Whole and Fractional Extracts of Cigarette Smoke and Those of Known Carcinogens on (1) The Cytology and Nuclear DNA Content of Epidermis in Various Strains of Mice and/or (2) The Cytology and Nuclear DNA Content of Lung and Epithelium of the Bronchial Tree of Mice and Hamsters (C)
R. H. RIGDON, M.D., *Professor of Pathology and Director, Laboratory of Experimental Pathology,* University of Texas Medical Branch, Galveston, Texas	Effects of Tobacco Smoke Condensate on the Respiratory Tract and Other Tissues of the Duck (P)
SYDNEY C. RITTENBERG, PH.D., *Professor of Bacteriology,* University of Southern California, Los Angeles 7, California	The Bacterial Degradation of Nicotine and Related Compounds. The Objective of the Project is the Elucidation of the Intermediary Metabolism of Nicotine Oxidation (P)
BENSON B. ROE, M.D., *Associate Professor of Surgery, Department of Surgery,* University of California School of Medicine, San Francisco 22, California	Study of the Action of Negatively Charged Ions on Tracheo-Bronchial Ciliary Action in the Human Patient
BENJAMIN A. RUBIN, PH.D., *Assistant Professor of Public Health and Preventive Medicine,* Baylor University College of Medicine, Houston, Texas (from the Wistar Laboratories, Philadelphia, Pennsylvania)	An Evaluation of the Phenomenon of Tumor Growth Enhancement as an Assay for Carcinogens Among the Polycyclic Hydrocarbons and Related Compounds (C)
WILLIAM O. RUSSELL, M.D., *Pathologist-in-Chief,* M.D. Anderson Hospital and Tumor Institute, University of Texas Medical Center, Houston 25, Texas	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi (C)

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GRANTEE AND INSTITUTION	PROJECT TITLE
PAUL D. SALTMAN, PH.D., *Assistant Professor of Biochemistry,* University of Southern California School of Medicine, Los Angeles 7, California	The Enzymatic Mechanism for the Dark Fixation of CO_2 by Tobacco (C—P) Some Aspects of Amino Acid Metabolism in Tobacco Leaves (C)
ALVIN R. SCHMIDT, PH.D., *Director of Counseling,* Tufts University, Medford, Massachusetts	Study of Attitudes Toward, as Well as Extent, Type and History of, Tobacco Smoking in a Young College Population. Study of Some of the Relationships of Smoking and Nonsmoking to Family History, Type of Secondary Schooling, Academic Interests, Academic Achievement, and Social Relationships Characteristics
ISAAC SCHOUR, D.D.S., PH.D., D.Sc., *Professor of Histology and Embryology and Dean,* University of Illinois College of Dentistry, Chicago 12, Illinois	Histologic Changes in the Oral, Pharyngeal and Nasal Tissues of Experimental Animals Subjected to Tobacco Smoke (C—P)
MAURICE S. SEGAL, M.D., *Clinical Professor of Medicine,* Tufts University School of Medicine, Boston, Massachusetts; *Director, Department of Inhalation Therapy,* Boston City Hospital, Boston, Massachusetts	Effects of Cigarette Smoking on Lung Function in Normal Subjects and Patients With Certain Respiratory Disease Conditions (C—P) Relationship of Cigarette Smoking to Chronic (Obstructive) Pulmonary Emphysema
CARL C. SELTZER, PH.D., *Research Fellow in Physical Anthropology,* Harvard University, Cambridge, Massachusetts	Morphology and Smoking in College Graduates: A Fifteen-Year Follow-Up Study (P) Harvard-Johns Hopkins Study of Body Form as Related to Smoking, and the Precursors of Hypertension and Coronary Artery Disease
CHARLES E. SHERWOOD, M.D., *Assistant Professor of Radiology,* University of Rochester School of Medicine and Dentistry, Rochester, New York	Investigation Into the Natural History of Carcinoma of the Lung With Particular Reference to the Radiographic Appearance of Such Processes, the Earliest Manifestation of Cancer on Chest X-Ray Photographs and the Tabulation of the Relationship of Smoking Habits and Occupation With the Incidence of Lung Cancer (C—P)
DAVID L. SIMON, M.D., *Instructor in Medicine and Fellow in Cardiovascular Research,* University of Cincinnati College of Medicine and Cardiac Laboratory, Cincinnati General Hospital, Cincinnati 29, Ohio.	The Effects of Chewing Tobacco on the Cardiovascular System of Man (C—P) The Effects of Pipe Smoking and Cigar Smoking on the Cardiovascular System of Man (C—P)
T. M. SONNEBORN, PH.D., *Distinguished Service Professor of Zoology,* Indiana University, Bloomington, Indiana	Checking and Extending the Stephano *Paramecium* Test for Carcinogenicity (C)
SAM SOROF, PH.D., *Research Associate,* The Institute for Cancer Research and Lankenau Hospital Research Institute, Philadelphia 11, Pennsylvania	Chemical and Physical Studies of the Tissue Proteins Involved in Chemical Carcinogenesis (C—P)

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GRANTEE AND INSTITUTION	PROJECT TITLE
FREDERICK J. STARE, PH.D., *Professor of Nutrition*, Harvard School of Public Health, Boston 15, Massachusetts	Experimental Studies of Cancer Utilizing a New Technique to See if Various 'Tars' Extracted From Tobacco May Incite the Formation of Lung Tumors (C)
MARION B. SULZBERGER, M.D., *Professor and Chairman, Department of Dermatology and Syphilology*, New York University-Bellevue Medical Center, New York 16, New York	Investigation of the Effects of Tobacco on the Human Vascular System, Based on the Fact that Certain Tobacco Effects are Due to Allergic Susceptibility of Specific Individuals Rather than to Obligatorily Toxic Products in Tobacco Smoke, and that Patients with Occlusive Vascular Diseases Respond Differently than Healthy Smokers (P)
CAROLINE BEDELL THOMAS, M.D., *Associate Professor of Medicine*, Johns Hopkins University School of Medicine, Baltimore 5, Maryland	The Significance of Different Individual Patterns of Circulatory Response to Cigarette Smoking (P) Studies of Genetic Differences Between Smokers and Nonsmokers (P). Studies of Psychological Differences Between Smokers and Nonsmokers as Shown by Comparison of Figure Drawings
TISSUE CULTURE ASSOCIATION (*President*, Dr. Margaret R. Murray, *Associate Professor of Anatomy*, Columbia University College of Physicians and Surgeons, New York, N. Y.)	To Assist in Establishment of Summer Training Course in Tissue Culture Techniques at University of Colorado Medical School, Denver, Colorado (C)
JANET TRAVELL, M.D., *Associate Professor of Clinical Pharmacology*, Cornell University Medical College, New York 21, New York	Effects of Nicotine in the Rabbit with Experimental Coronary Atherosclerosis (C—P)
E. D. WARNER, M.D., *Professor of Pathology*, State University of Iowa College of Medicine, Iowa City, Iowa	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi (C) Correlation of Bronchial Epithelial Changes with Comparable Changes in Other Organs—A Pathologic-Anatomic Study (C)
RICHARD L. WECHSLER, M.D., *Clinical Physiologist*, Montefiore Hospital Institute of Research, Pittsburgh 13, Pennsylvania	Effect of Cigarette Smoking on Cerebral Blood Flow, Cerebral Metabolism, Blood Gases, Blood pH, Arterial Pulse Pressure Curves, Electrocardiograms, and Electroencephalograms (C)
RUSSELL W. WELLER, M.D., *Pathologist*, Memorial Hospital of Chester County, West Chester, Pennsylvania; *Associate Professor of Pathology*, Hahnemann Medical College, Philadelphia 2, Pennsylvania	Pathologic-Anatomic Study of Cellular Changes in Human Bronchi A Selected, Extended and Detailed Study of Human Bronchial Mucosa

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GRANTEE AND INSTITUTION	PROJECT TITLE
SIMON H. WENDER, PH.D., *Research Professor of Chemistry*, University of Oklahoma Research Institute, Norman, Oklahoma	A Qualitative and Quantitative Study of the Individual Polyphenol Content of Cigarette Tobacco and of the Smoke and 'Tars' Resulting from Cigarette Smoking, and Also Study of the Fate of These Compounds in the Animal Respiratory System (C—P)
DUANE G. WENZEL, PH.D., *Professor of Pharmacology*, School of Pharmacy, University of Kansas, Lawrence, Kansas	The Determination of the Chronic Effects of Orally Administered Nicotine on Serum Cholesterol and Phospholipids; the Electrocardiographic Response to Ergonovine; and the Vascular Pathology of Cholesterol-fed Rabbits (C—P)
FREDERICK E. WHISKIN, M.D., C.M., *Director, Division of Health and Personality Equilibrium*, The Age Center of New England, Inc., Boston 16, Massachusetts (see Dibner)	Pilot Study of the Smoking Habits of Age Center Members (C)
J. EDWIN WOOD, M.D., *Professor of Medicine*, Medical College of Georgia, Augusta, Georgia	The Effect of Prolonged Inhalation of Tobacco Smoke and of Prolonged Abstinence from the Use of Tobacco on the Peripheral Vascular Response to Acute Inhalation of Tobacco Smoke in Man (C—P)
SUMNER WOOD, JR., M.D., *Assistant Professor of Pathology, Department of Pathology*, Johns Hopkins University, Baltimore 5, Maryland	Evaluation of Etiologic Factors, such as Occupational Hazards and Habits, and Pathologic Peculiarities in the Long-Term Survival of Patients Following Resection for Bronchogenic Carcinoma
JOHN P. WYATT, M.D., *Professor of Pathology*, St. Louis University School of Medicine, St. Louis 4, Missouri	An Investigation Into the Nature of the Pigmentary Lesion in Centrilobular Emphysema

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